Mini Review
Volume 12:10, 2022

Medicinal Chemistry

ISSN: 2161-0444 Open Access

Brown Adipose Tissue Activation Nutraceuticals

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Abstract

Obesity and its comorbidities have become pandemic, posing a challenge to the global healthcare system. To address such a public health burden, lifestyle changes, nutritional interventions, and pharmaceuticals should be combined in a personalised strategy. Obesity and glucose metabolism dysfunctions are exacerbated by altered brown adipose tissue function. Through uncoupled respiration, BAT thermogenic activity burns glucose and fatty acids to produce heat, which can dissipate excess calorie intake, reduce glycemia, and circulate fatty acids released from white adipose tissue. Thus, BAT activity is expected to contribute to overall energy homeostasis and protect against obesity, diabetes, and lipid profile changes. To date, clinical trials for pharmacological therapies aimed at activating brown fat have failed due to cardiovascular side effects or insufficient efficacy.

Keywords: Brown adipocyte • Thermogenesis • Microbiota • Phytochemicals

Introduction

Obesity prevalence has increased significantly over the last few decades. Obesity is linked to hormonal dysfunctions and systemic inflammation, which contribute to insulin resistance, dyslipidemia, hypertension, and metabolic syndrome, all of which increase the risk of cardiovascular disease. Currently, anti-obesity pharmacological approaches either reduce dietary fat absorption or decrease appetite. So far, pharmaceutical anti-obesity drugs' limited long-term efficacy and potential adverse effects have limited their use, and phytochemicals may represent appealing options in terms of negligible side effects and costs. Mammalian fat is classified into two types: white adipose tissue and brown adipose tissue. WAT is primarily responsible for storing energy as triglycerides, whereas BAT is responsible for dissipating energy as heat. BAT is present in rodents throughout their lives. Humans, though present in newborns and young children which generates heat by dissipating the proton gradient across the inner membrane of the mitochondria, causing ATP synthesis to be inhibited. Non-shivering thermogenesis is a type of thermogenic activity that helps regulate body temperature and burns calories. Cold exposure increases the activity of sympathetic nervous system fibres innervating BAT, which is a critical activation mechanism for BAT, promoting its thermogenic function. Interestingly, cold stimulation not only activates BAT depots but also induces the emergence of brown-like adipocytes in WAT depots, known as "beige" or "brite" adipocytes. This process, known as "browning of WAT,"results in the formation of beige adipocytes, which have morphological and thermogenic properties similar to classical brown adipocytes.

Literature Review

Pharmacological approaches aimed at increasing brown fat activity in humans could be a promising strategy for combating obesity and related metabolic diseases. Important endocrine axes can finely modulate BAT activation, which has implications for cardiometabolic health. On the other hand, growing evidence suggests that diet influences brown and beige adipocyte thermogenic activity, implying that diets with different macronutrient compositions may influence brown fat activity differently. Importantly, over the last two decades, a number of studies have identified several nutritional compounds capable of stimulating the thermogenic function of brown and beige adipocytes. This review will discuss a variety of nutraceuticals that have been shown to increase the thermogenic activity of adipose tissue while also providing hints about the molecular mechanisms by which such compounds modulate adipose tissue.

Bacteroides, Faecalibacterium, and Clostridium are able to produce and modulate total levels and relative proportions of specific short-chain fatty acids in the systemic circulation. Acetate and propionate are produced by several Bactericides genera, whereas butyrate is mostly produced by Firmicutes genera. Circulating has been proposed to regulate a variety of metabolic processes in various organs and tissues, including adipose tissue thermogenic function, at least in animal models. Acetate treatment of brown or white adipocyte cultures resulted in the induction of brown fat markers, and acetate or butyrate administration was able to stimulate beige adipocyte differentiation and BAT activation in mice.

Discussion

Obese mice treated with the flavonoid tangeretin lost weight, had less liver steatosis, and had better glucose metabolism. Notably, tangeretin treatment was able to change the composition of the gut microbiota and stimulate BAT activity, counteracting dysbiosis and decreasing the Firmicutes to Bacteroidetes ratio. In another study, mice fed the natural polymethoxyflavone nobiletin showed reduced obesity and induction of WAT browning, as well as a composition shift in the gut microbiota, with an increase in the abundance of Bacteroidetes and a decrease in the ratio of Bacteroidetes to Firmicutes. Transplanting the microbiota from nobiletin-treated mice to obese mice resulted in increased BAT activity, induction of beige adipocyte formation, and decreased obesity in the recipient animals.

Consider how retinoic acid and its metabolites act as transcriptional regulators and modulators of extranuclear signalling transduction cascades in different cell types to explain vitamin A's involvement in several critical physiological processes. Vitamin A and its metabolites regulate gene expression by modulating retinoic acid receptor transcriptional activity. Retinoic acid-responsive elements have been discovered in gene regulatory regions, and retinoic acid treatment of brown adipocyte cultures increased transcript levels. Retinoids primarily regulate transcription, though retinoic acid has been shown to activate p38 mitogen-activated protein kinase, which promotes transcription. Retinoic acid, on the other hand, was found in cultures to reduce

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Received: 03 October, 2022, Manuscript No. mccr-22-84888; **Editor Assigned:** 05 October, 2022, PreQC No. P-84888; **Reviewed:** 17 October, 2022, QC No. Q-84888; **Revised:** 21 October, 2022, Manuscript No. R-84888; **Published:** 27 October, 2022, DOI: 10.37421/2161-0444.2022.12.645

the expression of lipogenic transcription factors as well as intracellular lipid content.

A systematic review and meta-analysis of human studies on berberine supplementation found that taking this alkaloid reduced body weight, BMI, and waist circumference, indicating that it has anti-obesity properties. Other meta-analyses found that berberine consumption improved blood glucose metabolism in type 2 diabetes patients, as well as the lipid profile, with lower levels of total cholesterol, triglycerides, and cholesterol. If the beneficial effects of berberin in clinical trials can be attributed, at least in part, to its ability to promote brown fat function, this is an issue that needs to be addressed and further research is needed.

Several preclinical and clinical studies have shown that resveratrol administration has anti-obesity effects. There was a reduction in weight, BMI, fat mass, waist circumference, and insulin levels in MetS patients treated with resveratrol. Tabrizi et al. found that resveratrol administration reduces weight, fat mass, and BMI, implying that such effects may be mediated by BAT enhancement, despite the fact that modulation of adipose tissue thermogenic function has not been observed in humans. Resveratrol supplementation improved mitochondrial function but had no effect on BAT activity in subjects with type 2 diabetes [1-5].

Conclusion

A number of studies suggest that activating BAT thermogenesis is a novel strategy for combating obesity and related metabolic diseases. Due to the associated cardiovascular side effects, the use of pharmacological agents capable of activating human BAT has had limited success. As previously stated, specific nutraceuticals, as well as combinations of different compounds, have been found to induce thermogenic gene expression in animal models' adipose tissue. Preclinical research has revealed molecular targets and signalling pathways involved in brown/beige adipocyte thermogenesis that are modulated by dietary supplements. Nutraceuticals such as capsinoids, catechins, sympathomimetics, and flavonoids were found to induce up-regulated expression as well as increases in the thermogenic protein. In studies with obese rodents treated with phytochemicals, thermogenic activation of adipose tissue was associated with a reduction in white fat mass, indicating that such compounds can counteract excessive expansion of WAT through the activation of brown/beige adipocytes.

Acknowledgement

None.

Conflict of Interest

There are no conflicts of interest by author.

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How to cite this article: Lombardo, Stefania. "Brown Adipose Tissue Activation Nutraceuticals." J Med Chem 12 (2022): 645.