Transcriptomics expression analysis to unveil the molecular mechanisms underlying the cocoa polyphenol treatment in diet-induced obesity rats

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ABSTRACT

Cocoa polyphenol (CP), due to their biological actions, may be supplementary treatments for adipose tissue-fat gain. However, the molecular mechanism of CPs is still ambiguous. This study investigated the hypothesis that CP treatment modulates expressing of lipid metabolism genes in mesenteric white adipose tissue (MES-WAT). Sprague–Dawley (SD) rats were fed a low-fat (LF) or high-fat (HF) diet for 12 weeks. Thereafter, HFD rats (n = 10/group) were treated at a dose of 600 mg/kg bw/day CPs (HFD + CPs) for 4 weeks. DNA microarray analysis resulted in 753 genes of the 13,008 genes expressed. Bioinformatics tools showed CP treatment significantly decreased gene expression levels for lipogenic enzymes, while increased the mRNA levels responsible for lipolysis enzymes. CP administration differentially regulates gene expression involved in lipid metabolism in MES-WAT. These data unveil a new insight into the molecular mechanisms underlying the pharmacological effect of CPs on obesity biomarkers in obese rats.

1. Introduction

Adipose tissue is the hub of lipid storage in the form of triglycerides (TGs) or energy release in the form of fatty acid (FA) when demanded by any tissue in the body [12]. A lack of an energy homeostasis due to excess energy storage leads to increase white adipose tissue mass and the development of obesity [17]. However, the regulation mechanisms underlying these associations are much less known. Cocoa, the fruit of *Theobroma cacao* L., was widely used in traditional medicine as a pharmaceutical for blood pressure and cardiovascular prevention. Later, numerous cocoa-derived polyphenolic compounds (i.e. flavonoids and phenolic acids) have shown capacity of obesity preventing via adipose tissue reduction and hypolipidemia effects [18,28,31]. To date, no works have yet studied about the pharmacological effects of CPs on gene expression in diet-induce obese rats. The present study therefore was designed to investigate the hypothesis that CP administration affects expression of key genes related to lipid metabolism in the white adipose tissue of diet-induced obese rats. It has become commonly clear that several pharmaceutical drugs to treat obesity were largely not efficient in normalizing visceral obesity. Moreover, these medications most often coupled with side effects [4]. Therefore, finding new natural products to reduce visceral fat accumulation is highly beneficial for optimal and healthy treatment. A group of the pharmacological drugs to manage of metabolic related disease such as obesity and type 2 diabetes mostly act on the peroxisome prolifertor-activated receptors (PPARs).

The expression patterns of a number of target genes, many of these differentially regulate lipid metabolism and could be modulated by a variety of natural substances, e.g., fatty acids, vitamins, and polyphenols [1,13]. Genome-wide expression data have been clearly elucidated the crosstalk between adipogenesis cascade and various regulatory transcription factors both in vitro and in vivo. PPAR γ, for example, was shown to increase adipocyte hypertrophy or preadipocyte differentiation specific-genes, thereby promoting the obesity development. The hypertrophic adipocytes are frequently associated with a variety of signaling adipokines secretion such as adiponectin, leptin and resistin [26]. In clinical pharmacology, there are currently many classes of lipid-lowering drugs. The mechanisms of actions of these agents depend mainly on drug–transcription factor interaction. Sterol regulatory element-binding protein (SREBP) agonists (statins) are used to treat hypercholesterolemia via suppression HMGCoA reductase, a rate-limiting enzyme for cholesterol synthesis [15]. In the same context, PPARγ agonist thiazolidinediones (TZDs) are given to induce insulin sensitivity in adipose tissue and muscle of obese-diabetic patients, while agonists (fibrates) are given to medicate hyperlipidemia in patients by activate PPARα-target genes [9].

These transcription factors bind to the promoter region of specific genes, which in turn, increase their transcription and thereby the protein synthesis encoded by these genes [30]. A group of researchers found that a long-term high fat diet (HFD) supplementation decreased mRNA levels for lipogenic enzymes, AMP-activated protein kinase

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