Review

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Metabolic interplay between white, beige, brown adipocytes and the liver

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Summary

In mammalian evolution, three types of adipocytes have developed, white, brown and beige adipocytes. White adipocytes are the major constituents of white adipose tissue (WAT), the predominant store for energy-dense triglycerides in the body that are released as fatty acids during catabolic conditions. The less abundant brown adipocytes, the defining parenchymal cells of brown adipose tissue (BAT), internalize triglycerides that are stored intracellularly in multilocular lipid droplets. Beige adipocytes (also known as brite or inducible brown adipocytes) are functionally very similar to brown adipocytes and emerge in specific WAT depots in response to various stimuli including sustained cold exposure. The activation of brown and beige adipocytes (together referred to as thermogenic adipocytes) causes both the hydrolysis of stored triglycerides as well as the uptake of lipids and glucose from the circulation. Together, these fuels are combusted for heat production to maintain body temperature in mammals including adult humans. Given that heating by brown and beige adipocytes is a very-well controlled and energy-demanding process which entails pronounced shifts in energy fluxes, it is not surprising that an intensive interplay exists between the various adipocyte types and parenchymal liver cells, and that this influences systemic metabolic fluxes and endocrine networks. In this review we will emphasize the role of hepatic factors that regulate the metabolic activity of white and thermogenic adipocytes. In addition, we will discuss the relevance of lipids and hormones that are secreted by white, brown and beige adipocytes regulating liver metabolism in order to maintain systemic energy metabolism in health and disease.

Keywords: Lipid metabolism; Brown adipose tissue; White adipose tissue; Metabolic disease; Non-alcoholic fatty liver disease; Lipoproteins, Triglycerides; Hepatokines; Adipokines; Lipokines; Bile acids.
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Introduction

White adipose tissue (WAT) and liver form a metabolic unit

White adipocytes are connective tissue cells specialized in handling fatty acids and triglycerides (TGs) that unite to form large adipose tissue depots in distinct anatomical locations [1]. However, only two types are regarded as relevant for systemic metabolism: intra-abdominal (visceral) WAT and subcutaneous WAT. Most intra-abdominal WAT (mesenteric and omental WAT) lies in the splanchnic bed and drains into the liver via the portal vein [2]. A consequence of this anatomical location is a special metabolic relationship with the liver in such a way that metabolites and regulatory factors released from intra-abdominal adipocytes have a disproportionate impact on liver cells [2]. As discussed in the section 'Role of WAT in liver metabolism and non-alcoholic fatty liver disease', intra-abdominal adipocytes are also functionally distinct and this has important implications for physiology and disease development.

In fasting and in other catabolic states, visceral and subcutaneous WAT depots together with liver provides other organs with fatty acids. In WAT, free fatty acids (FFAs) are released by intracellular lipolysis of TGs from lipid droplets [3] and transported, bound to plasma albumin, to energy-consuming organs such as skeletal muscle and heart [3,4]. Lipolysis is mainly controlled by β-adrenergic signaling and cyclic adenosine monophosphate (cAMP)-dependent phosphorylation of lipid droplet proteins and activation of lipases [3] as a consequence of low insulin levels and high sympathetic tone in WAT. A large proportion of FFAs are taken up by hepatocytes, which esterify them to form complex lipids such as TG, cholesteryl esters and phospholipids. These are then secreted as part of very low density lipoproteins (VLDL) [5,6]. These TG-rich lipoproteins support particularly skeletal and cardiac muscles with fatty acids that are locally released by lipases bound to the luminal face of the endothelium, lipoprotein lipase (LPL) and, of minor importance for TG hydrolysis, endothelial lipase [3,7,8].

In the postprandial state, both WAT and liver again play a central role, as they are the primary destination of dietary fatty acids. These are directed to WAT by LPL-catalyzed, intravascular lipolysis of intestine-derived chylomicrons (CM) and to liver either as CM remnants or as LPL-derived FFA not taken up at the site of hydrolysis (spill-over) [9]. Insulin is the dominant regulator

increasing LPL activity in WAT. In addition, it suppresses intracellular lipolysis and thus the release of fatty acids into the circulation. These insulin actions ensure that in the postprandial state excessive fat is stored in adipocytes but not in the liver [7,10]. In liver, insulin reduces intracellular apolipoprotein B concentration, which together with diminished FFA influx as a consequence of insulin-dependent fatty acid retention in WAT causes reduced VLDL secretion and prevents inappropriate rises in plasma TG [11]. In addition to storing and distributing pre-formed, dietary fatty acids, both WAT and liver are major sites of *de novo* lipogenesis (DNL). Under conditions of surplus energy, they convert carbohydrates, amino acids and other non-lipids to saturated and monounsaturated fatty acids [12–14]. Another important hepatic action of insulin is the stimulation of DNL via activating the transcription factor sterol regulatory element binding protein-1c (SREBP1c). Teaming up with carbohydrate responsive element binding protein (ChREBP), a transcription factor activated by enhanced glucose metabolism, SREBP1c induces high liver expression of DNL enzymes in the fed state [14]. Similarly, insulin increases ChREBP activity and DNL in WAT via increased GLUT4-dependent glucose influx [15]. High glucose and insulin levels in the postprandial state thus ensure the conversion of surplus carbohydrates into energy-dense fatty acids, stored mostly as TG in WAT. Together, WAT and liver constitute a common fatty acid pool for storing energy and providing other organs with fatty acids. Insulin and catecholamines are the preeminent hormones regulating this metabolic unit.

Brown and beige adipocytes: an energy sink for thermogenesis

Brown adipose tissue (BAT) depots are considerably smaller by volume than WAT depots, especially in humans who display a much lower body surface to volume ratio than rodents and other small mammals. The depots are widely dispersed found at distinct locations in the body trunk. The largest and most extensively studied BAT depot of rodents is located between the shoulder blades (interscapular BAT), similar to the one found in newborn humans [16–18]. In addition to classical brown adipocytes present in BAT depots, beige adipocytes can be found in specific WAT depots such as subcutaneous WAT and perirenal WAT in rodents. These adipocytes are functionally very similar to brown adipocytes and tend to form small clusters in WAT depots after prolonged cold stimulation, a process known as browning of WAT [19]. Thermogenic adipocytes in adult humans are found at deeper sites, around the claviculae, the sternum, paravertebral, epicardial and perirenal positions. Although the thermogenic activity detected by increased glucose uptake using molecular imaging technologies is undisputed [20–22], the exact composition of these fat depots with regard to brown and beige adipocytes is still a matter of debate [23,24]. In contrast to WAT, BAT does not serve as an energy store for other organs. Rather, it uses the TGs stored in its numerous lipid droplets as fuel for adaptive, non-shivering thermogenesis [25]. Moreover, BAT is capable of taking up large amounts of fatty acids and glucose from the circulation when fully activated [25–27]. Brown and beige adipocytes display a high density of mitochondria, which contain a protein unique to these thermogenic adipocytes, uncoupling protein-1 (UCP1). This protein separates respiratory chain activity from ATP production by shunting protons through the inner mitochondrial membrane. BAT is highly innervated by the sympathetic nervous system which triggers brown adipocyte activation within hours upon cold stimulation [25,28]. In addition to this signaling originating from the central nervous system, endocrine and paracrine mediators of brown and beige adipocyte activation have been identified, for example liver-derived bile acids [29,30], cardiac natriuretic peptides [31] as well as locally released adenosine [32]. Activated brown and beige adipocytes significantly contribute to systemic metabolism by increasing energy expenditure through heat production. The relevance of BAT is exemplified by the fact that in rodents, BAT and liver take up equal amount of energy from the bloodstream, a process which is able to normalize glucose and lipid values in insulin resistant and hyperlipidemic mice [26,27,33].

Key points

- The liver and white adipose tissue (WAT) continuously exchange very low density lipoproteins (VLDL) and free fatty acids (FFA), respectively, forming a common fatty acid pool for storing and distributing energy. Together with insulin, and paracrine factors synthesized by adipose tissue, liver-derived apolipoproteins and angiopoetin-like proteins regulate peripheral VLDL processing in an organ specific manner.
- In the obese state, the liver produces regulatory peptides that modulate inflammation and insulin sensitivity in WAT. Conversely, hypertrophic WAT influences metabolic networks and inflammatory status in the liver through increased FFAs and altered secretion of lipid mediators and adipokines.
- Upon activation by cold, brown adipose tissue (BAT) and brown-like (beige) adipocytes recruited in WAT combust profound amounts of diet- and VLDL-derived fatty acids for heat production, a process controlled also by hepatic factors including bile acids.
- In the activated state, brown and beige adipocytes secrete endocrine factors, i.e. interleukin-6, insulin-like growth factor 1 and neuregulin-4 that regulate systemic and also specifically hepatic glucose and lipid metabolism. Although PET-CT studies provide evidence for a high catabolic activity, prospective studies need to define the relevance of thermogenic adipocytes for human liver metabolism and disease.

Hepatic factors regulating WAT and BAT function

As a major player in systemic metabolism the liver is tightly connected with adipose tissues, influencing lipid storage and metabolism through controlling metabolite fluxes to WAT and BAT (Fig. 1). In addition, regulatory molecules originating in the liver have been demonstrated to affect adipose tissue subclinical inflammation and insulin resistance, two important features of obesity and the metabolic syndrome.

Liver-derived factors controlling energy delivery

A major metabolic function of the liver is the production and redistribution of cholesterol and fatty acids, secreted in VLDL particles for the use by WAT and other organs. The liver not only provides VLDL lipids, it also synthesizes LPL-modulating proteins