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Metabokines in the regulation of systemic energy metabolism

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Abstract

Metabolism consists of life-sustaining chemical reactions involving metabolites. Historically, metabolites were defined as the intermediates or end products of metabolism and considered to be passive participants changed by metabolic processes. However, recent research has redefined how we view metabolism. There is emerging evidence of metabolites which function to mediate cellular signalling and interorgan crosstalk, regulating local metabolism and systemic physiology. These bioactive metabolite signals have been termed metabokines. Metabokines regulate diverse energy metabolism pathways across multiple tissues, including fatty acid β-oxidation, mitochondrial oxidative phosphorylation, lipolysis, glycolysis and gluconeogenesis. There is increasing impetus to uncover novel metabokine signalling axes to better understand how these may be perturbed in metabolic diseases and determine their utility as therapeutic targets.

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Introduction

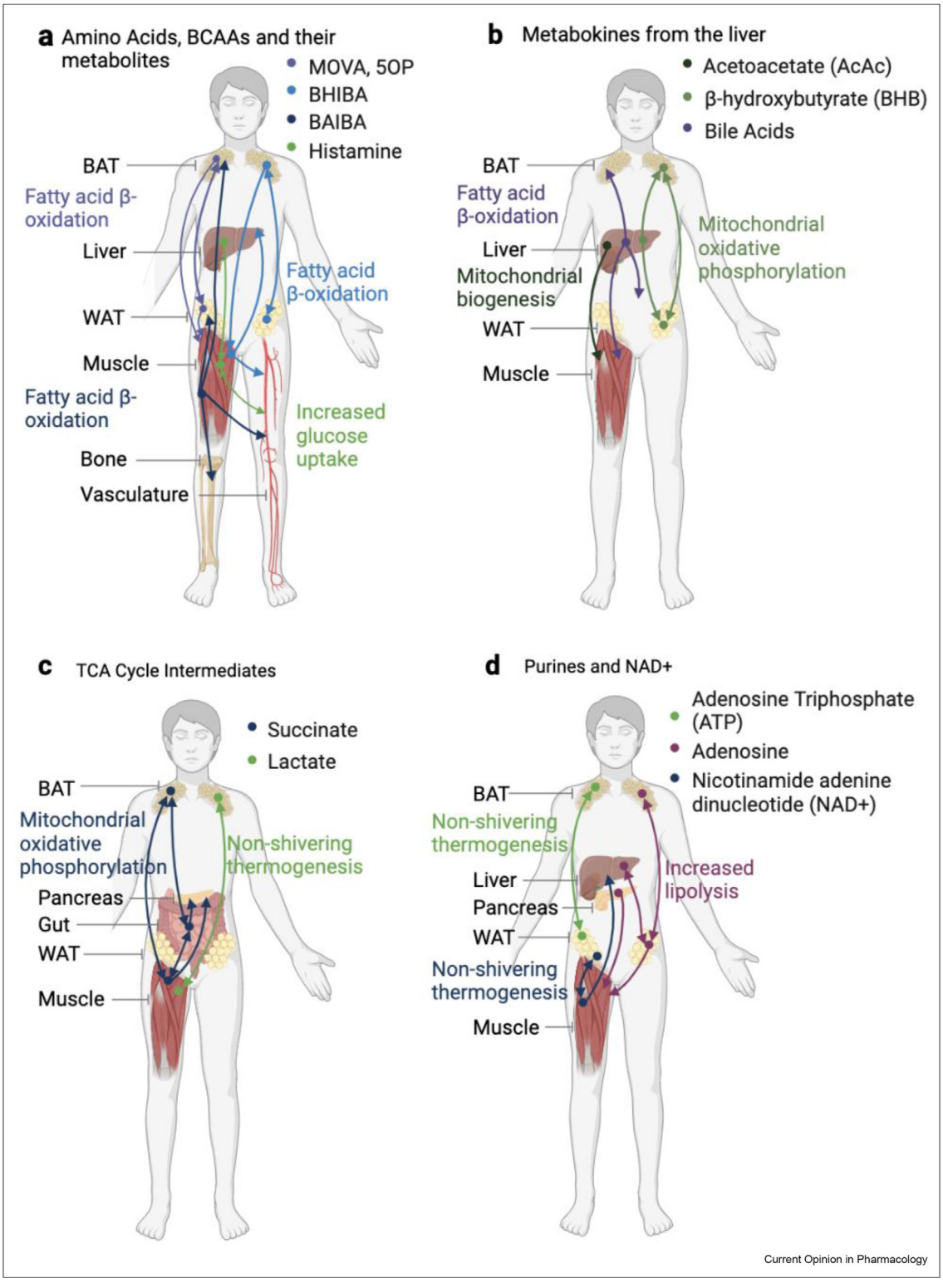
The Greek word from which metabolism derives, metabolē, means change. Traditionally, metabolites have been seen as passive participants changed by metabolic processes. Metabolites can provide the fundamental building blocks for the macromolecular structures of the cell, generating waste products of cellular catabolism or providing the fuel to meet the energy demands of these cellular activities. They are defined simply as the intermediates or end products of metabolism. However, this description falls short in conveying the biological role of many of these physiological small molecules. An emerging view suggests that many metabolites have an active part in regulating local metabolism and systemic physiology, beyond steady-state fluxes, through direct signalling mechanisms and interorgan crosstalk. Many of these metabolites fit an emerging class of bioactive molecules termed metabokines. A metabokine can be defined as an endogenously produced small molecular weight molecule with the ability to carry and elicit an autocrine, paracrine or endocrine signal to regulate local or systemic physiology and metabolism. They differ from vitamins, which often have a dietary source [1,2], and other signals which influence metabolism, such as protein cytokines [3,4], bioactive lipids [5] and lipokines [6], which have been reviewed thoroughly elsewhere. A great deal of recent research has focussed on understanding the roles of metabokines in the paracrine and endocrine regulation of systemic energy metabolism through key metabolic pathways, including fatty acid β-oxidation, mitochondrial oxidative phosphorylation, lipolysis, glycolysis and gluconeogenesis. This review will summarise some of these findings and discuss emerging metabokines which act to regulate aspects of cellular and whole-body energy metabolism in mammals.

Amino acids, branched-chain amino acids and their metabolites

Fatty acid β-oxidation can occur in any cell containing mitochondria, making it a key systemic pathway of energy metabolism. It is also a target of regulation by metabokines. The branched-chain amino acids (BCAAs) are three essential amino acids: leucine, isoleucine and valine. Increased BCAA catabolism has previously been observed to increase fatty acid β-oxidation via the tricarboxylic acid cycle (TCA) and glyceroneogenesis [7]. However, BCAAs and their metabolites also exhibit the ability to regulate cross-tissue fatty acid β-oxidation as metabokine interorgan signals (Figure 1a).

Brown adipose tissue (BAT) is a thermogenic tissue that can oxidise lipid and glucose to produce heat, whereas white adipose tissue (WAT) was traditionally considered as a lipid storage tissue. However, over the last few decades, WAT has been identified as an important endocrine organ that releases messengers termed adipokines, which regulate systemic physiology[8,9].

Figure 1



Systemic relationship of metabokines. **a.** Amino acid, branched-chain amino acid (BCAA) and BCAA metabolite-mediated metabokine signalling axes. **b**. Hepatic metabokine (ketone bodies and bile acid) signalling axes. **c.** Tricarboxylic acid (TCA) cycle metabokine mediated signalling axes. **d.** Purinergic metabokine signalling axes. Circles represent organ/tissue from which metabokine is produced, arrows indicate the direction of signals to target tissue. Metabokine signalling axes and the metabolic pathways they regulate are colour coded. Brown adipose tissue (BAT), white adipose tissue (WAT). Produced using Biorender.

Although beige adipose tissue is located within WAT depots, it exhibits an inducible BAT-like thermogenic phenotype. Interest in brown and beige adipose tissue has increased in recent years following the discovery of these tissue types in adult humans and their therapeutic potential for the treatment of obesity and cardiometabolic diseases [10,11]. One of the principal findings resulting from this increased research interest is that both brown and beige adipose tissue also function as endocrine organs releasing numerous protein, lipid and metabokine signals [8,9]. These signals create an interorgan signalling network between brown, beige and white adipose tissue and skeletal muscle [12–17].

The monocarboxylic acid, BCAA derivatives, 3-methyl-2-oxovaleric acid (MOVA) (a catabolite of isoleucine), β-hydroxyisobutyric acid (BHIBA) (a valine metabolite) and the amino acid 5-oxoproline (5OP) are secreted from brown and white adipocytes in response to thermogenic stimuli [12]. These metabokines were found to increase adipose tissue browning, and adipose tissue and skeletal muscle fatty acid β-oxidation in an adipose–adipose and adipose–skeletal muscle interorgan signalling axis, respectively [12]. MOVA and 5OP function to induce fatty acid oxidation through a cAMP–PKA–p38 MAPK signalling mechanism [12]. 5OP is a component of the metabolic pathway involved in regenerating the antioxidant glutathione and likely signals to communicate redox status and rescue systemic redox stress through browning of WAT [12]. BHIBA functions through the mammalian target of rapamycin (mTOR), regulates adipocyte and myocyte metabolic gene expression and induces fatty acid β-oxidation. BHIBA has also been identified as a metabokine signal released from skeletal myocytes in response to transgenic expression of the transcriptional regulator peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), often described as a master regulator of metabolism and the adaptive response of muscle to exercise [18]. On release from myocytes, BHIBA signals to endothelial cells, enhancing fatty acid uptake through regulating the trans-endothelial flux of fatty acids [19]. In murine models, MOVA, 5OP and BHIBA induce beige adipose tissue and BAT thermogenesis and WAT and skeletal muscle fatty acid oxidation, drive an increase in whole-body energy expenditure and subsequent resistance to weight gain.

Additionally, the valine catabolite, β-Aminoisobutyric acid (BAIBA) was identified as a metabokine released from skeletal muscle in response to both transgenic expression of PGC-1α and endurance exercise [20]. BAIBA contributes to a skeletal muscle – WAT – liver interorgan signalling axis. On release from exercising skeletal muscle, BAIBA concentrations increase in plasma, increasing the expression of BAT-specific genes and driving the browning response in WAT. In the liver, BAIBA acts to increase fatty acid β-oxidation through a PPARα-mediated mechanism. It has been determined that BAIBA also acts to attenuate hepatic endoplasmic reticulum stress [21]. Through these mechanisms, BAIBA increases whole-body energy expenditure, resistance to weight gain and improves glucose homeostasis [20]. More recently, BAIBA was identified as a key metabokine signal between skeletal muscle and bone during exercise, protecting osteocytes from mitochondrial reactive oxygen species (ROS)-induced apoptosis [22]. BAIBA acts as an exercise-mimetic signalling from muscle to the vasculature to relieve inflammation and oxidative stress through antioxidative properties [23]. Therefore, the metabokine BAIBA, released from skeletal muscle in response to exercise, contributes to several of the beneficial effects of exercise on health.

Metabolic risk of obesity and type 2 diabetes (T2D) is associated with increased circulating levels of BCAAs. The BCAAs are thought to contribute to metabolic disease progression through the regulation of protein synthesis and degradation, insulin secretion and energy balance [24–27]. Adipose tissue and skeletal muscle regulation of circulating BCAA levels mediates whole-body energy homeostasis [28,29]. BCAA catabolic enzymes are downregulated in adipose tissue both in obesity and insulin resistance [30]. Taken together, the metabolic risk associated with increased circulating BCAAs may, in part, be mediated by decreased biosynthesis and secretion of these brown/beige adipocyte and skeletal myocyte metabokines and perturbation of the interorgan signalling axes they mediate.

Beyond BCAAs, other amino acid-derived metabokines have been identified. Histamine is derived from the decarboxylation of the amino acid histidine. Histamine is synthesised through the activity of histidine decarboxylase (HDC) [31]. Within skeletal muscle, histamine primarily binds to two G protein-coupled receptors histamine receptor subtypes (H_1 and H_2) [32]. H_1 and H_2 receptors are located within endothelial cells, vascular smooth muscle cells, nociceptive afferent neurons in skeletal muscle and liver [33,34]. Histamine has been implicated in the systemic signalling induced by aerobic exercise [31,35]. During exercise, histamine is released from mast cells in the liver and skeletal muscle. The histamine then acts through autocrine and paracrine signalling within the skeletal muscle to signal to endothelial cells, vascular smooth muscle cells and afferent nociceptive fibres, triggering vasodilation and increased glucose availability and uptake into endothelial cells [36].

Metabokines from the liver: ketone bodies and bile acids act as metabolic signals

Ketone bodies are produced from acetyl-CoA derived from fatty acid β-oxidation in the liver. Fatty acids are mobilised from adipocytes and transported to the liver. In the liver, the fatty acids are converted into ketone bodies which can then be used as a glucose-sparing energy source [37]. The ketone metabolite class includes acetoacetate (AcAc) and β-hydroxybutyrate (BHB), the two primary ketones, as well as the less abundant acetone. AcAc is transported in the blood and is imported into cells during low carbohydrate conditions. Within the mitochondria, AcAc is reduced to acetyl-CoA and BHB, which is used as an energy source in the TCA cycle [38]. Recently, ketone bodies have been found not to simply serve as an energy source for the brain, heart and skeletal muscle, but they may also act as metabokines (Figure 1b).

AcAc acts as an antioxidant, attenuating the damaging effects of ROS. AcAc reduces the accumulation of ROS, specifically superoxide anion radical, without influencing mitochondrial respiration or oxidative phosphorylation by reducing lipid peroxidation [39] and increasing mitochondrial biogenesis through upregulation of PGC-1α [40,41]. AcAc has also been shown to regulate skeletal muscle regeneration by stimulating satellite cell activation and proliferation through mitogen-activated protein kinase (Mek)-extracellular signal-regulated kinase (Erk)-cyclinD1 pathway signalling in a Ras-independent manner [42].

BHB is the most abundant ketone in mammals and is primarily synthesised in the liver. However, BHB has recently been identified to be synthesised in BAT and WAT [43]. BHB is synthesised within beige adipose tissue and BAT from fatty acid oxidation during non-shivering thermogenesis and secreted from the adipocytes in a process regulated by the transcriptional regulator PR domain containing 16 (PRDM16) [44]. BHB can then act upon mitochondrial bioenergetics of adipose tissue. The secreted BHB increases mitochondrial biogenesis, uncoupled respiration and thermogenesis in adipocytes [44]. This increase in BHB levels can restore the loss of beige fat function typically associated with ageing [43]. The secreted BHB also acts on precursor stem cells to induce myofibroblast differentiation and promote beige adipocyte differentiation [43]. The ketone bodies, BHB and AcAc act as metabokines through the regulation of the mitochondria in adipose tissue and skeletal muscle.

Bile acids are produced by the liver as end products of cholesterol catabolism [45]. Bile acids signal through farnesoid X receptor (FXR), which regulates bile acid synthesis and secretion, as well as lipid and glucose metabolism in the liver (Figure 1b). Through FXR signalling, bile acids activate lipoprotein lipase, and lipolysis of triglycerides in triglyceride-rich lipoproteins and VLDL [46]. Decreased circulating bile acid concentrations results in decreased intestinal lipid absorption and increased lipid content of faeces [47]. Bile acid signalling through FXR also regulates hepatic glucose production and serum glucose levels through the suppression of hepatic phosphoenolpyruvate carboxykinase (PEPCK), glucose 6-phosphatase (G6Pase) and fructose 1,6-bisphosphatase 1 (FBPase) [48,49]. Ultimately, bile acids in the liver inhibit gluconeogenesis and promote glycogen synthesis. In the pancreas, bile acid signalling through FXR in β-cells induces insulin production and secretion [50].

Within BAT, bile acids increase thermogenesis through cyclic-AMP-dependent thyroid hormone activating enzyme type 2 iodothyronine deiodinase (D2) which increases oxygen consumption [51]. Increased cAMP levels in BAT activate thermogenic gene expression and enhanced glycolysis [52]. D2 has also been shown to regulate glucose uptake in skeletal muscle [51], and bile acids stimulate muscle growth and regeneration through cAMP signalling [53]. Bile acids bind to and activate G-protein-coupled receptor TGR5 which induces intracellular cAMP levels in BAT and skeletal muscle [54]. Within the muscle, bile acids stimulate muscle growth and regeneration through cAMP signalling [53].

TCA cycle intermediates

Succinate dehydrogenase catalyses the oxidation of succinate into fumarate in the TCA cycle. Succinate was once thought to only act as a respiratory substrate. However, recent studies suggest that succinate acts as a metabokine to regulate energy homeostasis (Figure 1c). Succinate has a tissue-specific mode of regulation. Circulating succinate increases thermogenic gene expression in BAT [21]. In BAT, succinate dehydrogenase activation drives non-shivering thermogenesis through mitochondrial ROS [55]. BAT responds to succinate by activating non-shivering thermogenesis reciprocally norepinephrine activation of BAT non-shivering thermogenesis increases circulating levels of succinate [55,56]. In the pancreas, succinate stimulates both insulin and proinsulin synthesis through succinate dehydrogenase [57]. Intestinal microbiota-produced succinate functions as a glucose precursor and activates intestinal gluconeogenesis, with beneficial effects on systemic energy homeostasis [58]. Gut microbiota is also a key producer of circulating succinate [56]. Elevated circulating succinate concentrations after anaerobic exercise drive fibre-type remodelling of skeletal muscle [59]. However, increased circulating succinate levels have also been observed in patients with chronic metabolic diseases, including obesity and T2D [60,61] and non-alcoholic fatty liver disease [62,63]. The relationship between succinate's apparent function to induce

Table 1

Table summarising the tissue of origin, target tissue and the function of metabokine signals.

Type	Metabokine	Tissue origin	Target tissue	Function	Pathway
Amino acids, branched-chain amino acids and their metabolites	3-methyl-2-oxovaleric acid (MOVA)	White and brown adipocytes	BAT, beige, WAT and skeletal muscle	Increases fatty acid β-oxidation	cAMP–PKA–p38 MAPK; redox stress [12]
	5-oxoproline (5OP)	White and brown adipocytes	BAT, beige, WAT and skeletal muscle	Increases fatty acid β-oxidation	cAMP–PKA–p38 MAPK; extracellular receptors [12]
	β-hydroxyisobutyric acid (BHIBA)	White and brown adipocytes and skeletal myocytes	BAT, beige, WAT, skeletal muscle [12] and endothelial cells [19]	Increases fatty acid β-oxidation [19]	Mammalian target of rapamycin (mTOR) [12]
	β-Aminoisobutyric Acid (BAIBA)	Brown adipocytes and skeletal muscle [20]	BAT, beige, WAT, skeletal muscle [20], liver [21], bone [22], endothelial cells [23]	Increases fatty acid β-oxidation [12]	Muscle with increased PGC-1α fatty acid β-oxidation [20]
	Histamine	Mast cells within skeletal muscle and liver	skeletal muscle [35], endothelial cells, vascular smooth muscle cells and afferent nociceptive fibres	Increases glucose uptake	histidine decarboxylase (HDC) [31]
Liver-derived metabokines: ketone bodies and bile acids	Acetoacetate (AcAc)	Liver	Skeletal muscle	Mitochondrial biogenesis	Upregulation of PGC1a [40,41]
	β-hydroxybutyrate (BHB)	Liver	BAT, beige, WAT	Fatty acid oxidation	PRDM16 [44]
	Bile acids	Liver	BAT, intestines, liver and muscle	Mitochondrial oxidative phosphorylation [51]	cAMP signalling [53]
TCA cycle intermediates	Succinate	BAT, skeletal muscle, intestine	Pancreas [57], BAT [21], intestine [56], skeletal muscle [59]	Mitochondrial oxidative phosphorylation	Succinate dehydrogenase
	Lactate	BAT, muscle	BAT, muscle	Non-shivering thermogenesis	MCT1 [65,66]
Purines	Adenosine triphosphate (ATP)	BAT and WAT	BAT and WAT	Non-shivering thermogenesis [73]	PANX1 [73]
	Adenosine	BAT, WAT, pancreas, liver	BAT, WAT, pancreas, muscle [78,79], liver [77]	Increased lipolysis	cAMP to increase lipolysis [75,76]
	NAD+	Muscle, adipose	Liver, muscle	Gluconeogenesis [84]	Sirtuin 1 [81]

metabolic health benefits and its association with metabolic disease is yet to be reconciled. Succinate's ability to act in a tissue-specific manner highlights the flexibility and specificity through which metabokines can regulate systemic energy metabolism.

Lactate was canonically considered a waste product of anaerobic metabolism. More recent research suggests that lactate acts as a metabokine by feeding into the oxidative metabolism of several tissues, mediating systemic metabolism as an intercellular and interorgan redox carrier (Figure 1c) [64]. BAT uses lactate derived from both intracellular glycolysis, and from the circulation through enhanced lactate import, to fuel non-shivering thermogenesis [65,66]. Lactate functions in a skeletal muscle − BAT signalling axis during exercise. Lactate is transported through monocarboxylate transporters (MCTs). Exercise training increases the expression of MCT1 in BAT by two-fold suggesting a lactate-dependent metabolic relationship between muscle and BAT during exercise [67,68]. The increase in BAT lactate utilisation could be a metabolic sink for increased levels of lactate released into the blood during exercise. Regular exercise increases mitochondrial biogenesis within skeletal muscle through the activation of MCT1, increasing systemic metabolic flexibility [69].

Regulation of purinergic signalling and NAD^+

Purinergic signalling regulates cellular function through the activation of purinergic receptors on cellular membranes. Extracellular signalling is mediated by purine nucleotides and nucleosides such as adenosine triphosphate (ATP), uric acid and adenosine (Figure 1d).

ATP is often thought of solely as a unit of cellular energy, rather than as a signalling molecule. ATP was also once thought to be limited to release from 'purinergic' nerves [70] and vasculature in the paracrine regulation of vasodilation [71,72], we now know that many cells have a basal release of ATP, indicating its involvement in extracellular ATP signalling, responsible for both physiological and pathophysiological responses. Basal release of ATP signal is dependent on cell type. Within adipose tissue, ATP is released from Pannexin 1 (PANX1) an ATP-permeable channel that can be activated via β3-adrenergic signalling within BAT [73]. Within adipose tissues, extracellular ATP acts as an autocrine and paracrine signal regulating adipocyte function by inducing thermogenic gene expression, lipolysis, lipogenesis, adipokine secretion, glucose uptake, adipogenesis and cell proliferation [74]. The deletion of PANX1 increases susceptibility to insulin resistance and obesity [73].

Adenosine also functions as a purinergic signal. Within adipose tissue adenosine is released through two mechanisms, the breakdown of ATP released from sympathetic nerves or directly from brown adipocytes [75,76]. Adenosine acts through adenosine receptors which trigger cAMP to increase lipolysis, beiging and insulin resistance in adipocytes [77]. Adenosine promotes adipogenesis and regulates insulin-dependent glucose uptake in skeletal muscle through the activation of A1 receptors [78,79]. Adenosine also acts on the liver to increase glycogenolysis, lipogenesis, gluconeogenesis and impair fatty acid oxidation and inflammation [77]. The complete understanding of the extent of adenosine systemic signalling is yet to be determined [80].

Oxygen is a key metabolic mediator that cannot be directly transferred; instead, electrons from redox reactions use pyridine nucleotides as carriers. Nicotinamide adenine dinucleotide (NAD^+) is an electron carrier in the oxidation of hydrocarbon fuels. NAD^+ is also the rate-limiting substrate for the sirtuin (SIRT) family of deacetylases, which function as metabolic sensors [81]. Within the liver, SIRT-1 regulates the deacetylation of PGC-1α, reactivating PGC-1α signalling [82]. NAD^+ levels fluctuate with nutrient availability, and during intense exercise, NAD^+ levels increase as a by-product of muscle pyruvate utilisation [83]. Under conditions of high nutrient and therefore low NAD^+ levels, PGC-1α is heavily acetylated and therefore inactivated, decreasing hepatic gluconeogenesis, adipose tissue thermogenic gene expression and skeletal muscle glucose uptake [84].

Conclusion

In this review, we have focussed on the discussion of metabokines with key roles in the regulation of the pathways of energy metabolism (Table 1). This review is not comprehensive, and many more metabokines are emerging with relevance to the maternal environment influencing both maternal and foetal metabolism [85] and the metabolism of the immune system [86]. Much like the transformative nature of metabolism itself, these emerging studies have highlighted a need for a change in the way metabolites and metabolic signalling are considered. It is increasingly clear that many molecules once thought of as passive intermediates of metabolism function as important regulators of systemic physiology. There is an increasing incentive to uncover novel metabokines and their regulatory axes to better understand how these pathways may be perturbed in metabolic diseases and determine their therapeutic potential.

Credit author statement

Amanda MacCannell and Lee Roberts have equally contributed to:

-Conceptualisation.

-Literature search.

-Validation and visualisation.

-Writing, editing, review.

Conflict of interest statement

The authors declare they have no conflict of interest.

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