Metabolism and Translational Medicine

REVIEW ARTICLE

Metabolic medicine: The mechanism of metabolic influence on diseases of various systems

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ABSTRACT

Metabolism affects or is influenced by almost every other biological activity. With the deepening of medical research, understanding the nature of natural metabolism is the primary means to solve complicated diseases. Therefore, starting from metabolism, starting from the root, starting from the pathophysiological basis, and realizing the transformation from the underlying mechanism to clinical medicine will be the way that the scientific research community must go for a long time in the future. This review mainly discusses that metabolites produced by some major metabolic pathways, such as glucose metabolism, lipid metabolism, and amino acid metabolism, are important signal transmitters and regulators of activity. It expounds on the role of metabolism in various system diseases, including cardiovascular system diseases, nervous system diseases, endocrine system diseases, and intestinal microbial system diseases, from the levels of metabolites, proteins, organelles, tissues, and systemic physiology.

Key words: metabolic medicine, metabolism, cardiovascular system, nervous system, intestinal flora

INTRODUCTION

Core metabolism can include rich carbohydrates, fatty acids (FAs), and amino acid nutrients, these nutrients to the human body's energy balance and macromolecular synthesis are essential. The core metabolic modes can be conveniently divided into three categories: synthesizing simple molecules or aggregating them into more complex macromolecules, causing molecules to breakdown to release energy or small metabolites, and those that help eliminate toxic waste from other pathways. Most cells in the decision-making process and metabolic changes are closely linked, so only the cell or tissue, in the case of a change in metabolism, changes its biological activity. This leads to the fact that disturbance of the metabolic process or metabolite abundance will affect the normal function of cells and even the whole body, thus inducing the occurrence and development of diseases. The past decade has revealed many parts of metabolites and metabolic pathways that could not be predicted from traditional biochemical understanding. Metabolism affects or is influenced by almost every cellular process, there is no longer any room in the study of biology that is entirely free from the influence of metabolism. Metabolism is the fulcrum of biology, so metabolic disorders underlie most acute, chronic,

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infectious, and noninfectious human diseases. This review discusses metabolites as important signal transmitters and activity regulators. It expounds on the critical role of metabolism in various system diseases, including cardiovascular, nervous, endocrine, and intestinal microbial system diseases, from the levels of metabolites, proteins, organelles, tissues, and systemic physiology. Fluctuations in metabolism are the essence of disease.

CARDIOVASCULAR DISEASES (CVDS)

In the past few decades, CVD has become essential to myocardial energy metabolism in regulating cardiac function and has received increasing attention. Since the heart is the most metabolically demanding organ in the body, it is not surprising that disturbed cardiac energy metabolism is a significant contributor to many CVDs. In addition, changes in substrate metabolism in many organs caused by CVD can also lead to changes in the metabolic profile of patients. This requires a broader understanding of the molecular functional changes that occur in CVD.

Heart failure

Branched-chain amino acids (BCAAs)

BCAAs composed of leucine, isoleucine, and valine, are essential amino acids and play a key role in protein synthesis and energy metabolism in the body. The oxidative metabolism of BCAAs occurs widely in skeletal muscle, fat, liver, kidney, and myocardium. Studies have shown that BCAAs metabolism is closely related to CVD occurrence, development, and prognosis.[1] Plasma BCAAs and their metabolites may become potential biomarkers for diagnosing CVDs, and BCAAs metabolic enzymes can also become new therapeutic targets for CVDs to improve heart function.

Impaired cardiac energy metabolism is a significant factor in the development of heart failure and a key determinant of its progression. The heart consumes a large amount of energy daily, and abnormal nutrient metabolism can affect the process of myocardial remodeling and the function of the normal myocardium. Defects in BCAA catabolic activity and elevation of BCAAs are emerging metabolic and molecular features associated with heart failure.[2] Research suggests that high BCAAs and branched-chain amino acid ketoacids (BCKAs) cause BCAAs oxidative damage and can be used as signaling molecules in heart failure, negatively impacting cardiac energy metabolism, which harms cardiac function.[3] Studies have shown that plasma leucine and isoleucine concentrations are higher in patients with chronic heart failure than in healthy people.[4] In the failing hearts of mice with pressure overloading-induced heart failure, BCAA metabolites accumulated, key BCAAs catabolic groups and the expression of branched-chain alpha-keto acid dehydrogenase (BCKD) phosphatase 2Cm (P2Cm) were downregulated.[5] Abnormal accumulation of BCAAs metabolites caused by defective BCAAs catabolism is an independent risk factor for cardiac systolic function damage. BCAA metabolites can activate the mammalian target of rapamycin (mTOR) signaling pathway, leading to reactive oxygen species (ROS) and mitochondrial dysfunction and accelerating heart failure caused by pressure overload.[5]

Therefore, different approaches have been developed to enhance cardiac BCAAs oxidation and reduce plasma BCAA levels in preclinical models of heart failure.[5–8] After 3,6-dichloro-2-benzothiophene carboxylic acid (BCKD kinase inhibitor) treatment of heart failure mice, BCAAs oxidation was increased, cardiac ejection fraction was raised, and cardiac function was improved.[8] Stimulation of the mitochondrial branched-chain aminotransferase (BCATm) enzyme is one of the potential targets for promoting BCAA oxidation and reducing myocardial BCAAs accumulation. Acute inhibition of systemic branched-chain aminotransferase (BCAT) with an orally active BCAT inhibitor resulted in a significant increase in plasma BCAA levels, indicating impaired systemic BCAA oxidation.[9] Thus, increasing flow through the BCATm increases BCAA oxidation and decreases cardiac BCAA levels, which may have a beneficial effect in reducing adverse remodeling in failing hearts. Recent studies have found that heart-specific BCATm deletion results in a selective increase in cardiac BCAA levels, triggering cardiac hypertrophy by stimulating the mTOR signaling pathway. In addition, myocardial-specific BCATm deletion significantly reduced myocardial BCKA levels and increased insulin-stimulated myocardial glucose oxidation rates.[10] However, it should be emphasized that increasing flow through the BCATm may increase cardiac BCKA levels. This is interesting because we have shown that BCKAs have an inhibitory effect on cardiac insulin signaling and insulin-stimulated glucose oxidation rates *in vitro*.[10] However, inhibition of BCATm activity may lead to the accumulation of BCAAs, which triggers mTOR signaling and leads to cardiac hypertrophy.[10] Therefore, targeting BCATm may not be a reasonable approach to treating heart failure, although this needs to be investigated directly.

Another route to target BCAA oxidation is through the stimulation of the BCKD. Increased flux through branched-chain ketoacid dehydrogenase (BCKDH) promoted BCAA oxidation and decreased BCAA and BCKA levels compared to BCATm. 3,6-dichlorobenzene-[b]thiene-2-carboxylic acid (BT2) is an allosteric inhibitor of the branched-chain ketoacid dehydrogenase kinase (BCKDK) that increases the

oxidation of BCAAs by inhibiting the phosphorylation of BCKDH and enhancing the activity of BCKDH.[11] Thus, BT2 improved cardiac function and attenuated adverse remodeling in a mouse model of ischemic and failing hearts by promoting the oxidation of BCAAs in the heart and the whole body. However, the contribution of accelerated systemic BCAA metabolism to the cardiac protection established by BT2 treatment is unclear. However, studies have shown that BT2 treatment reduces the accumulation of cardiac BCAAs.[8,12] In addition, BCAA and BCKA supply to the heart can be reduced through diet intervention. Restriction of BCAAs in the diet of Zucker fat rats to promote FA utilization is beneficial for cardiac adenosine triphosphate (ATP) production and triglyceride level reduction. However, the mechanism is still unclear.[13] In addition, recent studies have shown that weight loss during lifestyle interventions enhances BCAA catabolism and improves insulin sensitivity in obese adolescents.[14]

With further research on the relationship between abnormal metabolism of BCAAs and heart failure, plasma BCAA levels may be used for the diagnosis and prognosis of heart failure. In addition, dietary and pharmacological interventions that enhance cardiac BCAA oxidation and limit cardiac BCAA and BCKA accumulation are cardioprotective in ischemic heart disease and heart failure.[3] Therefore, targeting cardiac BCAA oxidation may be a promising treatment for heart failure.

Glucose metabolism

Glucose transport into myocytes is regulated by specific transmembrane glucose transporters (GLUTs) localized to the sarcolemma.[15] The expression levels of GLUT-1 and GLUT-4 were positively correlated with glucose uptake. Heart failure progression is characterized by enhanced utilization of glucose rather than FAs, and in end-stage heart failure, the heart becomes unable to use both substrates efficiently.[16] During glycolysis, glucose is rapidly converted to glucose-6-phosphate in the cytoplasm, oxidized to pyruvate, and transported into mitochondria *via* the tricarboxylic acid (TCA) cycle to produce ATP. Several studies have reported that mitochondrial glucose oxidation is defective in the failing heart.[17] Elevated circulating lactate levels may result from increased glycolysis and the failure of the failing heart to oxidize the increased pyruvate produced by glycolysis, as pyruvate dehydrogenase activity is reduced in heart failure.[18] In a rat model of compensatory cardiac hypertrophy, myocardial glycolysis rather than myocardial glucose oxidation increases.[19] In contrast, the rate of myocardial glucose oxidation increased during the compensated phase of myocardial hypertrophy in the left ventricular press-overload rat model. At the same time, it decreased during the decompensated phase of heart failure.[19] It is generally accepted that alterations in glucose utilization may vary depending on heart failure pathology and stage.[16] This hypothesis is supported by reduced levels of circulating glucose, glucose 1-phosphate, glucose 6-phosphate, lactate, citrate, succinate, succinyl-coenzyme A (succinyl-CoA), and fumarate in patients with end-stage heart failure. After implantation of a left ventricular assist device (LVAD), circulating glucose and lactate levels increase in the nonfailing heart.[20]

FA metabolism

Acylcarnitines are derivatives of fatty acyl-coenzyme A (acyl-CoA), reflecting changes in the rate of FA oxidation and specific defects in the mitochondrial β-oxidation machinery. Elevated levels of circulating acylcarnitine in patients with end-stage heart failure are associated with an increased risk of mortality and rehospitalization due to FAs.[21] As a result, circulating long-chain acylcarnitines decreased after implantation of LVAD.[21] Consistent with these findings, circulating long-chain acylcarnitines are increased in patients with heart failure and preserved ejection fraction. Even higher levels were found in heart failure patients with reduced ejection fraction.[22] However, Body *et al.* found that acylcarnitine was reduced in the myocardial tissue of patients with end-stage heart failure at the time of heart transplantation or implantation of a LVAD compared with the myocardial tissue of patients without a history of heart failure.[23] This study recruited only patients with heart failure without diabetes, whereas other studies included a large proportion of patients with heart failure with diabetes. Circulating acylcarnitines are frequently elevated in obese and diabetic patients, which may explain the differences between the studies above.[16] Myocardial acylcarnitine reduction may represent the impaired mitochondrial function and FA oxidation.[24] FA oxidation and protein expression were slightly decreased in compensated heart failure but significantly reduced in decompensated heart failure.[24] Thus, many differences in acylcarnitine metabolism can be explained by the severity of heart failure, underlying diabetes or obesity, and an overall decline in left ventricle (LV) function.[18] Future metabolomics studies could consider these aspects and make obvious comparisons between these subgroups of patients with heart failure.

Ketone body metabolism

Ketone bodies can be degraded to acetyl-CoA, potentially maintaining mitochondrial respiration in the heart. Ketone bodies play a minor role in cardiac energy production under physiological conditions, but their contribution to energy production increases as circulating ketone levels increase.[25] However, previous studies have shown changes in the ability of the human

heart to extract certain circulating ketone bodies due to the effects of left ventricular dysfunction. The levels of circulating β-hydroxybutyrate and acetone in patients with heart failure are significantly increased, while the concentrations of β-hydroxybutyrate and acetone in myocardial tissue are significantly decreased.[26] On the other hand, ejection fraction keeps the heart failure patients' serum ketone-like acetoacetate, alpha hydroxybutyric acid, and β-hydroxybutyric acid concentrations lower than in patients who did not have heart failure.[27] In addition, patients with heart failure without preserved ejection fraction have lower serum ketone levels than those with preserved ejection fraction,[27] which may indicate that changes in ketone metabolism depend on the degree of heart failure. Therefore, patients with severely reduced left ventricular function (< 35%) had lower plasma β-hydroxybutyrate levels than patients with less reduced left ventricular function and healthy controls.[27] In addition, β-hydroxybutyric-CoA levels were higher in the myocardial tissue of patients with end-stage heart failure, demonstrating impaired oxidation in heart failure. The increased expression of metabolites downstream of ketone body oxidation and the simultaneous upregulation of critical enzymes in the ketone body pathway suggest an increased energy dependence of the failing heart on ketones, compensating for the decreased myocardial FA oxidation.[23] For example, diabetic patients in the empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes mellitus (T2DM) (EMPA-REG outcome) study treated with sodium-glucose cotransporter two inhibitors showed a significant reduction in heart failure-related rehospitalizations. Elevated ketone bodies have been discussed as one of the possible cardioprotective mechanisms for improving cardiac efficiency.[28]

Coronary heart disease (CHD)

BCAAs

Coronary artery disease is a complex disease caused by multiple factors and is one of the leading causes of death worldwide. Studies have shown that plasma BCAA concentration is a risk factor for the onset of coronary artery disease independent of blood glucose, blood pressure, blood lipids, and body mass index and is positively correlated with the occurrence and severity of coronary artery disease[29] and is independently associated with increased carotid intima-media thickness.[30] Elevated serum BCAA levels are an independent risk factor in middle-aged and elderly Chinese patients with metabolic syndrome and CVD, and the development of CVD is significantly accelerated in patients with elevated serum BCAA levels.[31] Serum BCAA levels are closely related to left ventricular diastolic dysfunction,[32] while plasma BCAA levels are independently associated with the severity of coronary artery disease.[29] High plasma BCAA in patients with ST-segment elevation myocardial infarction is associated with an increased risk of in-hospital adverse cardiovascular events after percutaneous coronary intervention.[33] The above clinical studies have directly proven the clinical predictive, diagnostic, and prognostic value of BCAAs in peripheral blood for CHD.

Many primary research results have shown that BCAAs have direct adverse effects on the heart. The plasma BCAA concentration increases after myocardial infarction, and the accumulation of BCAAs aggravates pathological remodeling and dysfunction after myocardial infarction in an mTOR-dependent manner.[6] BCAA accumulation can inhibit glucose metabolism and exacerbate the decline in insulin sensitivity after myocardial infarction and the susceptibility of the heart to ischemia-reperfusion injury.[7] BCAA accumulation can promote cardiomyocyte apoptosis and enhance caspase-3 activity, leading to oxidative stress and superoxide generation and aggravating myocardial ischemia-reperfusion injury.[34] Acetyl-CoA and propionyl-CoA, the end products of BCAA metabolism, are involved in the propionylation modification of tropomodulin 3 (TMOD3). Propionylation modifies lysine 255 of TMOD3, increasing platelet activity and promoting arterial thrombosis formation. It increases the risk of CHD.[35] Studies have shown that the hexosamine biosynthesis pathway (HBP) and O-glycosylated protein modification can protect cardiomyocytes from various stresses and play a protective role in the heart. The long-term accumulation of BCAAs caused by catabolic defects leads to the downregulation of HBP expression. Reducing its modification of protein O-glycosylation leads to the loss of the protective effect of O-glycosylated protein modification on the heart,[36] and reducing O-glycosylation can inhibit the activity of pyruvate dehydrogenase complex protein, thereby reducing the utilization rate of glucose by cardiomyocytes, which may be the critical factor of myocardial infarction.[7] Studies have shown that 3,6-dichloro-2-benzothiophene carboxylic acid can significantly reduce myocardial infarction injury, inhibit BCKD phosphorylation, significantly improve BCAA decomposition disorder, reduce cardiac dysfunction and inhibit myocardial remodeling after myocardial infarction.[6] In summary, BCAA, by activating mTOR, induced myocardial glucolipid metabolism disorder and mitochondrial dysfunction for CHD pathological processes.

Glucose metabolism

During ischemia, the rate of glucose oxidation decreases, accompanied by an increased rate of glycolysis due to the stimulation of glycogenolysis. Myocardial lactate concentration increased with the severity of ischemic

time.[16] In diaphragm ablation in patients with acute ischemia caused by CHD or alcohol, lactic acid increased circulating levels reflect myocardial metabolism of anaerobic glycolysis increase. This is also the case in patients undergoing coronary angioplasty for stable angina. Over 1 min of ischemia, the circulating lactate level increased after 10 min due to balloon inflation.[37] Low oxygen levels in ischemia inhibit aerobic oxidation and reduce the TCA cycle of metabolites, the cause of which are products such as fumaric acid and succinic acid production.[38] The production of ROS induced by reperfusion is regulated by tissue succinate levels.[39] Mouse models simulating ischemia-reperfusion injury have shown that succinate accumulates in ischemic heart tissue, and succinate oxidation is a critical factor in mitochondrial ROS accumulation and damage.[39]

Reperfusion therapy for acute myocardial infarction can cause adverse reactions such as ischemia-reperfusion injury. Mitochondria play an essential role in ischemia-reperfusion injury. Under the stimulation of ischemia and hypoxia, a variety of signaling pathways are activated in cardiomyocytes, which affect the uncoupling of the mitochondrial respiratory chain, the opening of the membrane permeability transition pore, and the release of cytochrome C, leading to disordered and damaged mitochondrial dynamics.[40,41] Mitochondrial damage leads to a significant accumulation of ROS and the release of intracellular lysosomes, which causes cell necrosis and apoptosis and even affects adjacent cardiomyocytes to expand the area of myocardial infarction. After myocardial injury, mitochondrial DNA (mtDNA) is released into the blood. Free mtDNA can induce Toll-like receptor 9-dependent activation of nuclear factor-κB (NF-κB), causing sterile inflammation and thereby exacerbating tissue damage. The level of mtDNA in blood circulation is significantly increased in patients with acute myocardial infarction, and the change in mtDNA copy number in mitochondria will also affect the function of mitochondria,[42] aggravate myocardial infarction and affect myocardial repair.

The impairment of mitochondrial energy metabolism efficiency and function can lead to the production of a large amount of ROS, which will damage mitochondrial structure and function, leading to the further deterioration of cardiac function. In heart failure, the body overactivates the sympathoadrenal system, and the sympathetic nerve releases norepinephrine to aggravate the work of the heart, causing excessive accumulation of Ca^{2+} and opening of the mitochondrial permeability transition pore (MPTP), leading to electron leakage in the process of transmission. Abnormal mitochondrial dynamic balance aggravates myocardial energy metabolism disorder. Studies have reported that the Hippo signaling pathway is activated during stress and affects the downstream Yes-associated protein 1 (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), which regulates cardiac metabolism under physiological and pathophysiological conditions. However, the molecular mechanism mediating metabolic remodeling is still unclear.[43] Schiro *et al.* reported that peroxisome proliferators-activated receptors (PPARs), estrogen related receptor (ERR), and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) affected myocardial energy metabolism at the transcriptional level, resulting in impaired cardiac function and myocardial remodeling and leading to heart failure.[44]

FA metabolism

In ischemic myocardium, the rate of FA oxidation decreases with decreasing oxygen supply because β-oxidation of FAs is dependent on oxygen for energy production.[16] In patients with CHD without heart failure, circulating medium-chain and long-chain acylcarnitines can predict subsequent cardiovascular events independent of established predictors.[45] However, their origin and pathophysiology during the progression of CVD are unknown. One possible explanation is that peroxisomes are involved in this process. Usually, long-chain dicarboxylic acids are oxidized mainly in mitochondria, and peroxisome oxidation of long-chain acylcarnitines may be a compensatory mechanism for metabolizing long-chain FAs in the linear chain during the progression of CVD.[46] Elevated levels of several plasma FAs, including palmitic, stearic, linoleic, and oleic acids, have been found in patients with ST-segment elevation myocardial infarction, suggesting ischemic alterations in cardiac energy metabolism.[47] Elevated FAs such as eicosapentaenoic and eicosapentaenoic acids may reflect ongoing inflammation during myocardial infarction.[48] The β-oxidation mechanism of the unsaturated FA linoleic acid seems to be hindered during myocardial infarction, leading to myocardial ischemia.[49] Thus, short-chain acylcarnitines are elevated in patients with significant ischemia, and aspartate decreases.[50] In addition, the sphingomyelin pathway, sphingomyelin, and ceramides were at higher levels in patients with angina than in healthy patients and patients with angina.[51] These results are supported by findings in which sphinganine, an intermediate in sphinganine biosynthesis, is elevated during acute myocardial infarction.[49] Sphingolipids and their derivatives are components of cell membranes that play essential roles in vascular maturation, atherosclerosis, and wound healing. In myocardial infarction, sphingolipid metabolism appears to be impaired, leading to increased CVD and obesity.[52] Glycerophosphatides are precursors of lipid mediators that appear to decrease during myocardial infarction, namely, phosphatidylserine, linoleamide glycerophosphatidylcholine, Lyso-PC (C18:2), Lyso-PC (C16:0), and Lyso-PC (C18:1).[49]

Phosphatidylcholine is hydrolyzed and oxidized to prostaglandins, thromboxanes, and prostacyclin by cyclooxygenase and cytochrome P450. These factors play critical roles in inflammation, immune response, and blood pressure control.[53] In conclusion, there is strong evidence that lipid metabolism is altered during ischemia.

CENTRAL NERVOUS SYSTEM DISEASES (CNSDS)

In the past few decades, there has been a surge of interest in the microbiome revolution among the scientific community. Advanced technological developments have enabled researchers to conduct more detailed investigations into gastrointestinal microorganisms and their metabolites, presenting opportunities to answer important questions that were previously unresolved. The human body is inhabited by trillions of microorganisms, which include bacteria, archaea, viruses, and fungi. Of these, 95% reside in the gut,[54] making the gut microbiota a primary area of research. In addition to its critical metabolic and protective functions, such as aiding digestion and preventing pathogen invasion, the gut microbiota plays a significant role in promoting epithelial cell growth and differentiation, and the development and maintenance of the immune system.[55] Through the microbiota-gut-brain axis, which establishes bidirectional communication between the gut and brain *via* neural, immune, endocrine, and metabolic signaling pathways, the gastrointestinal microbiota also influences central nervous system (CNS) function and human behavior. Research indicates that abnormalities in gut microbiota composition are linked to several neuropsychiatric disorders, including stroke,[56] autism spectrum disorder,[57] depression,[58] Parkinson's disease (PD),[59] and Alzheimer's disease (AD).[60] This underscores the importance of maintaining a healthy gut microbiome for overall health and wellbeing. Below, we will focus on the relationship between key metabolites of the gut-brain axis (GBA) and AD, stroke, and cognitive impairment.

Cognitive disorder

Dementia is considered to be an age-related disease. Dementia is the presence of memory impairment combined with at least one other cognitive impairment that significantly impacts daily activities. Worldwide, 40 million people live with dementia, which is expected to double every 20 years to more than 110 million by 2050.[61] The most common type of dementia is AD, which accounts for at least 60% of all cases. Vascular dementia is the second most common form of dementia and is estimated to account for approximately 20% of patients.[62]

There is increasing evidence that diabetes predisposes individuals to cognitive decline leading to dementia in animal models and in humans with Type 1 diabetes mellitus (T1DM) and T2DM.[63,64] Of the components of metabolic syndrome, hyperglycemia is most strongly associated with the risk of developing cognitive impairment.[65] Diabetes in midlife is associated with a 19% increase in cognitive decline over 20 years compared with individuals without diabetes.[66] A recent pooled analysis of 14 studies examined data on 2.3 million people and more than 100,000 dementia cases from cohorts in Asia, Europe, and the Americas. Studies have found that diabetes is significantly associated with an approximately 60% increased risk of dementia.[67] AD may therefore represent a distinct form of brain-specific insulin resistance resulting from impaired glucose regulation.[68] An essential function of insulin in the brain is regulating mitochondrial targeting signal (MTS) in the presynaptic hippocampus. Amyloid can attenuate the effects of insulin on synaptic terminal mitochondrial (Mt) and deplete energy reserves required for synaptic plasticity, learning, and memory,[69] similar to the proposal that Mt function is reduced in AD, cognitive dysfunction may be due in part to cortical hypometabolism and area-specific decline in glucose utilization and impaired insulin signaling.[70]

Glucose metabolism

Although the brain represents only a tiny fraction of our body weight (about 2%), it has an exceptionally high energy demand on the brain itself, using more than 20% of glucose-derived energy.[71] Glucose metabolism is often required for neuronal communication. Requiring energy from ATP to trigger action potentials, restoring postsynaptic possibilities, and maintaining ionic gradients, neurons consume 75% to 80% of the brain's energy.[72] The brain cannot produce or store glucose itself, so it relies on the glucose produced in the body by the food we eat, which can be stored as glycogen in astrocytes to power metabolic processes. Therefore, energy metabolism must be tightly controlled to maintain optimal brain function. Indeed, glucose metabolism disturbances in the brain have been observed in dementia and neurodegenerative diseases, including AD and PD.[73] Several abnormalities in AD have been suggested to play a role in causing brain damage and resulting clinical signs and symptoms, including impairment of energy/oxidative metabolism.[74] Impairment of energy/oxidative metabolism is associated with damage to cerebral circulation, damage caused by ROS or other free radicals, and intrinsic defects in the major pathways of energy/oxidative metabolism. These pathways include the TCA cycle and electron transport.[75]

Amyloid-β (Aβ) is central to the pathogenesis of AD, and vascular dysregulation, as well as reduced endothelial

GLUT1, are mechanisms by which Aβ may exert its deleterious metabolic effects. In addition, alterations in brain aerobic glycolysis are usually observed early in the course of AD.[76] A significant function of aerobic glycolysis is maintaining high levels of glycolytic intermediates to support anabolic reactions within the cell. L-serine is a nonessential amino acid produced by transferring the glycolytic intermediate 3-phosphoglycerate (3PG) to the phosphorylation pathway. L-serine is the precursor of D-serine, a coagonist of synaptic N-methyl-D-aspartic acid receptors (NMDARs), and is required for synaptic plasticity.[77] It has been found that the synthetic pathway of L-serine is impaired in young AD mice and AD patients, and AD mice show lower occupancy of NMDAR coagonist sites and synaptic and behavioral deficits. Similar defects have been observed following the inactivation of the L-serine synthesis pathway in hippocampal astrocytes, supporting a critical role for L-serine in astrocytes. Dementia due to AD is also characterized by early and progressive metabolic disturbances, as observed with [^{18}F]-fluorodeoxyglucose positron-emission tomography (FDG-PET). FDG-PET changes precede brain atrophy and neuronal dysfunction.[78] L-serine treatment during pregnancy and after birth improves fetal brain growth and prevents neurological symptoms, and dietary L-serine supplementation prevents synaptic and behavioral deficits in AD mice.[79] These findings suggest that exogenous L-serine can compensate for the deficiency of de novo production in the brain and suggest oral administration of L-serine as a readily available treatment for AD.

Short-chain fatty acids (SCFAs)

Growing evidence indicates that SCFAs can regulate the CNS physiology and behavior of the host,[80–82] SCFAs can affect the brain and behavior *via* various molecular mechanisms, such as inhibition of histone deacetylase (HDAC), induction of enteroendocrine signaling, vagus nerve (VN) activation, and anti-inflammatory properties.[83] Propionate and butyrate both inhibit HDAC activity, leading to changes in gene expression and ultimately suppression of tumor formation and inflammatory signaling in various tissues.[84] These actions of propionate and butyrate are mediated through activation of the G-protein-coupled receptor (GPR) 41 and GPR 43. Besides the colon, GPR 41 is also highly expressed in adipose tissue, while GPR 43 is highly expressed in immune cells.[85]

Germ-free (GF) mice exhibit increased blood-brain barrier (BBB) permeability due to reduced expression of tight junction proteins, including occludin and claudin-5, which can be alleviated by SCFAs.[86] Furthermore, treatment with SCFAs can improve the defective morphology and maturation of microglia in GF mice.[87] SCFAs produced by the gut microbiota can cross the BBB *via* the circulation system and influence microglia function and maturation, thereby controlling their function.[88] Administration of sodium butyrate to GF mice resulted in increased expression of occludin, and exposure of GF adult mice to the gut microbiota led to increased expression of claudin-5 by brain endothelial cells.[86] Sodium butyrate has been shown to confer neuroprotection by decreasing microglial activation through reducing pro-inflammatory mediators and increasing anti-inflammatory mediators in activated microglia.[89] Additionally, administration of SCFAs to a pig model demonstrated an increase in neurogenesis, granular cell layer size, and changes in glucose metabolism in the hippocampus.[90] Finally, butyrate treatment reversed reduced blood circulation and functional connectivity, elevated microglial activation in the hippocampus, and impaired spatial memory in a diet-induced obese, low-density lipoprotein receptor transgenic mouse model.[91]

Tryptophan

Serotonin is a neurotransmitter synthesized from tryptophan by tryptophan hydroxylase (TPH) enzyme in the enterochromaffin cells. The gut microbiota can modulate serotonin production, as certain bacteria and microbial metabolites stimulate its production. This impacts homeostasis, especially gut motility and platelet function. Additionally, studies show that GF rats have decreased serotonin levels.[92] Microbial modulation also plays a role in kynurenine production *via* the tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) enzymes. The gut microbiota indirectly influences kynurenine production by regulating glucocorticoid production and immune system activation of IDO.[93]

Indole and its derivatives are produced by microbiota in the intestinal lumen and act as ligands for aryl hydrocarbon receptor (AHR), a transcription factor involved in the immune response and inflammation inhibition in the gastrointestinal tract. Activation of AHR regulates T-cell differentiation and inhibits intestinal inflammation.[94] Indole derivatives have been reported to cross the BBB and activate AHR in astrocytes to inhibit the NF-κB pathway and suppress pro-inflammatory responses.[95] Indole-3-propionic acid (IPA), an indole derivative, acts as a ligand for pregnane X receptor (PXR) and downregulates enterocyte tumor necrosis factor-alpha (TNF-α) while upregulating junctional protein-coding mRNAs. IPA protects CNS neurons from oxidative and ischemia-induced neuronal damage.[96] Modulation of the microbiota through oral bacteriotherapy and fecal transplantation has anti-inflammatory and antioxidant effects, improves cognitive and behavioral performance in AD patients.[97]

Trimethylamine N-oxide (TMAO)

TMAO, a microbially derived metabolite, has been implicated in metabolic, cardiovascular, and cerebrovascular diseases. A recent study showed that TMAO is measurable in the cerebrospinal fluid (CSF), suggesting that this microbiota-derived metabolite can reach the CNS and may therefore be associated with neurological function or dysfunction.[98] Indeed, mice treated with dietary TMAO exhibit increased brain aging and cognitive impairment, possibly due to increased oxidative stress, mitochondrial dysfunction, and inhibition of mTOR signaling.[99] The underlying etiology of AD is highly complex and multifactorial. Multiple genetic and environmental factors have been implicated in the pathogenesis of AD, including contributions from the gut microbiota. It has been hypothesized that TMAO may be related to AD pathology.[100] An investigation confirmed that the gut microbiota-deposited metabolite TMAO was elevated in the CSF of patients with mild cognitive impairment (MCI) and AD dementia, and CSF TMAO levels were correlated with CSF biomarkers of AD pathology and neuronal degeneration.[101] These results provide additional evidence for the link between TMAO and AD and shed further light on the role of gut microbiota in AD. However, longitudinal studies are needed to determine whether elevated TMAO during midlife predicts the subsequent development or worsening of AD pathology. In this context, drugs that inhibit gut microbial TMAO production may help slow AD pathology.

Ischemic stroke

Ischemic stroke is a permanent infarction of brain tissue resulting from a sudden loss of cerebral blood flow that leads to impairment of normal neurological function. Cerebral arteries are occluded by emboli or *in situ* thrombosis, followed by disruption of oxygen and energy supply, and ischemic stroke leads to irreversible neuronal damage and a cascade of molecular reactions.[102] Cerebral ischemia induces a series of biochemical and cellular responses in which the efficiency and function of mitochondrial energy metabolism are impaired, the efficiency of the oxidative respiratory chain is affected, electron leakage occurs, and mitochondrial ROS production is increased. Oxidative stress caused by excessive ROS production plays a vital role in the basic pathological progression of brain injury in ischemic stroke.[103] Oxidative stress occurs when the intrinsic antioxidant potential of ROS is insufficient, and the endogenous redox balance cannot be maintained. When oxidative stress occurs, ROS can cause cytotoxicity through oxidative damage to lipids, proteins, and nucleic acids, resulting in detrimental consequences on the structure and function of brain tissue.[104]

TMAO is a kind of waste material from gut microbes, trimethylamine by liver flavin single oxygenase transformation. Since TMAO is a potential pathogenic factor for various CVDs, its use as a biomarker has attracted considerable research interest.[105] However, there are few studies on the association between TMAO and stroke. A nested case-control study in a Chinese hypertensive population showed that higher TMAO levels were associated with an increased risk of the first stroke. Patients in the highest third had a 34% higher risk of the first stroke than those in the lowest third. They also found that patients with low folate and high TMAO had the highest incidence of stroke.[106] In patients with a first stroke, elevated TMAO levels are associated with the risk of stroke recurrence and subsequent cardiovascular events in a dose-dependent manner. This relationship persisted even after adjustment for traditional cerebrovascular risk factors and the severity of the initial stroke. The blood TMAO concentration is closely related to the number of proinflammatory intermediate $CD14^{++}/CD16^{+}$ monocytes.[107] A case-control study of Chinese patients with stroke and transient ischemic attack (TIA) revealed significant dysregulation of the gut microbiota. Importantly, plasma TMAO concentrations were lower in stroke and TIA patients than in control patients with asymptomatic atherosclerosis. They examined TMAO levels in patients who already had a stroke or TIA, which were relatively low compared to previous Western studies, and treatment of stroke or TIA may reduce TMAO levels.[108]

Hemorrhagic apoplexy

Hypercholesterolemia has been well documented as a modifiable risk factor for ischemic stroke. At present, lipid-lowering therapy with statins has been widely used in patients with ischemic stroke. However, concerns have been raised about the concomitant risk of hemorrhagic stroke, mainly intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), which may be associated with reduced serum cholesterol concentrations.[109] An inverse relationship between serum cholesterol levels and increased risk of hemorrhagic stroke was revealed in earlier studies. Subsequently, in a multiple risk factor intervention trial, it was found that the risk of fatal cerebral hemorrhage in patients with serum total cholesterol (TC) less than 4.13 mmol/L was three times higher than that in patients with serum TC higher than 4.13 mmol/L.[110] A total of 23 prospective studies with 143,141 participants were included, and 7960 (5.6%) hemorrhagic strokes occurred. The overall relative risk of hemorrhagic stroke in the high-low analysis was 0.69 (95% confidence interval [CI], 0.59 to 0.81) for TC, 0.98 (95% CI, 0.80 to 1.19) for high-density lipoprotein cholesterol (HDL-C), and 0.62 (95% CI, 0.41 to 0.92) for low-density lipoprotein cholesterol (LDL-C). In dose-response analyses, the overall relative risk of hemorrhagic stroke for

an increase of 1 mmol/L in TC was 0.85 (95% CI, 0.80 to 0.91), for HDL-C was 1.11 (95% CI, 0.99 to 1.25), and for LDL-C was 0.90 (95% CI, 0.80 to 0.91). The pooled relative risk of ICH with HDL-C was 1.17 (95% CI, 1.02 to 1.35). Total cholesterol levels were inversely associated with the risk of hemorrhagic stroke. Increased LDL-C levels appear to be associated with a reduced risk of hemorrhagic stroke. HDL-C levels appear to be positively related to the risk of ICH.[111] Another prospective cohort study of 267,500 Chinese individuals reached a similar conclusion that TC, LDL-C, and triglycerides were positively associated with ischemic stroke. The risk of hemorrhagic stroke was higher when TC was below 120 mg/dL. LDL-C and triglycerides were not associated with hemorrhagic stroke. The ischemic and hemorrhagic stroke risk may be higher when HDL-C is below 50 mg/dL.[112]

METABOLIC DISORDERS

Diabetes

Diabetes is a series of metabolic disorders of protein, fat and electrolyte caused by absolute or relative insufficient insulin secretion and reduced sensitivity of target tissue cells to insulin,[113] which can be divided into T1DM, T2DM, gestational diabetes mellitus and other types of diabetes mellitus, T2DM being the most common. The cause of diabetes is related to genetic or dietary factors, and it is expected to provide new therapeutic strategies and targets for diabetes through metabolic medical intervention of glucose metabolism, amino acid metabolism, lipid metabolism and intestinal flora in diabetic patients.

Although there is evidence that supplementation or intake of BCAA from a BCAA-rich diet improves metabolic health, higher plasma BCAA has been found in animal models and in patients with T2DM,[114] and in clinical studies, Increased BCAA levels are positively correlated with insulin resistance.[115] BCAA has emerged as a potential biomarker for predicting the future risk of T2DM[116] and plays an important role in the pathogenesis and progression of diabetes. According to the most popular theory, increased accumulation of BCAAs, especially leucine, leads to overactivation of mechanistic target of Rapamycin complex 1 (mTORC1) and impaired insulin action. Some scholars also believe that it is not BCAAs themselves, but their catabolic damage related to reduced expression of genes encoding catabolic enzymes of BCAAs, resulting in the accumulation of toxic metabolic intermediates, leading to pancreatic beta cell dysfunction, stress signal transduction and cell apoptosis.[117] In addition, the synergistic effect of excess BCAAs and lipids may underlie the transition from obesity to T2DM, as chronic elevation of BCAAs and circulating FAs may enhance the state of chronic hyperinsulinemia and the continuous secretion pressure of islet beta cells, leading to islet beta cell dysfunction.[118]

In T2DM, when the islet secretion is insufficient, glucose metabolism disorder is the first cause. At this time, the oxidative phosphorylation of glucose in the cell is reduced, which leads to the decrease of glycolysis, pentose phosphate bypass and TCA circulation, and the decrease of glycogen synthesis and the increase of decomposition. The above metabolic disorders reduce the ability of liver, muscle and adipose tissue to take up and utilize glucose, increase the output of fasting and postprandial liver glycogen, increase the supply of gluconeogenic substrates and enhance the activity of phosphoenolpyruvate carboxylase, increase liver gluconeogenesis, and also cause fasting and postprandial hyperglycemia.[113,119]

Patients with T2DM often present with characteristic plasma lipids and lipoprotein abnormalities, including HDL-C, often normal LDL-C levels but with a predominance of small dense LDL particles, and elevated triglyceride levels.[119] The dyslipidemia of T2DM is related to insulin resistance and is often an early manifestation of it, occurring even before overt diabetes develops. The predominant triglyceride containing lipoprotein is very low-density lipoprotein (VLDL). The liver synthesizes VLDL, and its production is stimulated by increased delivery of free fatty acids (FFAs), also called non-esterified fatty acids (NEFA), to the liver. In patients with normal insulin sensitivity, insulin acutely inhibits VLDL secretion from the liver, but when insulin resistance is present, the chronically elevated insulin levels make the liver resistant to the inhibitory effects of insulin on VLDL secretion, thus even when insulin levels are high, VLDL secretion remains high.[118] In addition, in insulin resistant states, there appears to be defective clearance of VLDL cholesterol primarily due to the decreased activity of tissue lipases, many of which are regulated by insulin. Lipoprotein lipase (LPL) is one of the most important tissue lipases regulating lipoprotein levels, and lower activity of LPL results in decreased clearance of VLDL.[120] Insulin resistance also causes reduced FFA absorption and enhanced lipolysis by adipocytes both of which cause increased circulating FFA levels. The increased FFA delivery to peripheral tissues (such as the liver and intestine) in conjunction with insulin resistance lead to overproduction of both hepatically and intestinally derived triglyceride-rich lipoproteins. Furthermore, increased levels of FFAs themselves can also cause insulin resistance.[121] This may lead to a vicious cycle of insulin resistance and FFAs potentiating each other.

Saturated FAs are associated with an increased risk of diabetes, while unsaturated FAs are negatively associated with diabetes.[122] In addition, in a prospective study,

monounsaturated FAs were associated with diabetes risk, while polyunsaturated FAs represented by n-6 FA were associated with reduced diabetes risk. Linoleic acid (the dominant n-6 polyunsaturated FA) was consistently associated with a lower risk of diabetes in analyses using different genetic variants and analytical methods.[123] FAs can be extracted from dietary triglycerides and phospholipids, and dietary controls have been shown to alter circulating FAs levels. Because of the possible causal relationship with diabetes, FA may be emerging as a new intervention target for diabetes prevention.

Intestinal microbiota is composed of many microbial species that affect human physiology and participate in different biological processes. They can regulate the immune system and inflammatory response, regulate intestinal barrier integrity and human metabolism, and participate in metabolite synthesis. Microbes in the gut produce many metabolites that contribute to the physiology of healthy individuals. However, changes due to genetic and acquired factors (such as age, nutrition, lifestyle, genetic predisposition, or underlying disease) can affect the proportion of metabolites produced by the gut microbiome, resulting in metabolic disturbances and ultimately disease.[124] A better understanding of the gut microbiome has been shown to play an important role in the development of diabetes, and recent studies have shown that changes in ecological dysregulation can promote insulin resistance and T2DM. A high-fat diet can induce up to three times the production of lipopolysaccharide (LPS) (from gram-negative bacteria) in a mouse model, leading to low inflammation and insulin resistance.[125] In addition, intestinal flora imbalance reduces SCFA synthesis that promotes intestinal barrier integrity, islet beta cell proliferation, and insulin biosynthesis. Ecological imbalance also affects the production of other metabolites, such as branched amino acids and trimethylamine, thus disrupting glucose homeostasis and triggering T2DM development.[126] Understanding the clinical significance of the gut microbiome is a relatively new field and further research is needed to better elucidate the association between the gut microbiome and T2DM.

Obesity

Obesity is defined as excessive accumulation or abnormal distribution of body fat (BF), which affects health. Under normal conditions, skeletal muscle and liver cells store monosaccharides in the form of glycogen. In obesity, excess glucose is converted into triglycerides through adipogenesis and stored in lipid droplets in fat cells. Over the past few decades, obesity has become a growing public health problem worldwide. Obesity has become a major public health problem because of its prevalence in both developed and developing countries and its major complications such as diabetes, CVD, respiratory failure and cancer.[127] Finding effective treatment and prevention methods to lose and maintain weight, thereby reducing the prevalence of obesity is an important health topic.

Both animal and human studies have shown that BCAAs play an important role in the pathogenesis of obesity and diabetic metabolic disorders. Felig *et al.*[128] first reported the phenomenon of higher circulating BCAA levels in obese individuals. More recently, it has been reported that plasma concentrations of BCAA are increased in older subjects with higher BF, suggesting that elevated BCAA can also be found in obese older adults, but that the specific body composition is characterized by an increase in both fat and lean mass.[129] Dysfunctional mitochondrial BCAA catabolism could explain the toxic effect of large amounts of BCAA catabolic metabolites accumulation in plasma of insulin-resistant obese people on cell function. These include BCAA-derived acylcarnitine (C3 and C5), 3-hydroxyisobutyric acid (3-HIB), 2-hydroxybutyric acid (2-HB), and 2-ketobutyric acid (2-KB).[130] Acylcarnitine has been shown to cause mitochondrial dysfunction. In addition, several studies have linked the accumulation of toxic metabolites due to defective BCAA catabolism to increased lipid toxicity. 3-HIB is a catabolic intermediate of valine that leaves mitochondria by covalently binding to CoA.[131]

Obesity has a complex and multifactorial etiology, and a growing number of preclinical studies support the notion of bidirectional signaling within the GBA mediated by metabolic, endocrine, neurological, and immune system mechanisms in the pathophysiology of obesity. Because the gut-microbiome-brain axis plays an important role in regulating obesity-related behaviors and body functions, targeting this pathway is a novel approach to treating obesity. Some intestinal bacteria can alter the secretion of intestinal hormones to further influence the hypothalamic neuroendocrine pathway on appetite and satiety.[132] Studies have also shown an association between *probiotics* and weight loss in animals and humans. In obese individuals, poor diet leads to an increase in the ratio of *Firmicutes* to *Bacteroidetes*.[133] This appears to help extract energy from the food consumed and increase energy storage in the host's adipose tissue. *Probiotics* have been proposed for weight loss through a variety of mechanisms.[134] *Probiotics* help restore tight connections between epithelial cells, thereby reducing intestinal permeability, preventing bacterial migration, and reducing inflammation from LPS sources. Reduced inflammation leads to increased hypothalamic insulin sensitivity, which improves satiety.[134]

Thyroid disease

Thyroid disease is one of the common endocrine

disorders. The diagnosis of thyroid disease is based on structural abnormalities of the gland and changes in secretory function. Hypothyroidism is one of the most common endocrine disorders, affecting 5%–10% of the global population.[135] People living in developed countries are more susceptible to autoimmune diseases, including Hashimoto's thyroiditis (HT) and Graves' disease (GD). HT is the most common cause of primary hypothyroidism.[136] GD, on the other hand, is the most common cause of hyperthyroidism. The thyroid gland produces hormones that control the function of most tissues and maintain the body's internal balance. Recent metabolomics studies have shown that in the pathogenesis and development of thyroid diseases, a variety of metabolic pathways and metabolites in the human body can exert varying degrees of influence,[136] mainly including glycolipid metabolism, amino acid metabolism, intestinal flora metabolism, *etc.* Glycolipid metabolism is closely related to the incidence of thyroid diseases, which is also an important reason why patients with T1DM have a higher risk of suffering from autoimmune thyroid diseases (AITD).[137]

The levels of various carbohydrate metabolism indicators in AITD patients are higher than those in normal population, including purine metabolites, *etc.*, indicating that the pathogenesis of AITD patients may be closely related to the disorder of carbohydrate metabolism.[136] Studies have shown that thyroid hormones have direct effects on lipid synthesis and metabolism by stimulating FFA.

The decomposition of white adipose tissue, the main source of acid, and the promotion of peripheral tissue to the intake of FFAs, thus affecting FA metabolism. Thyroid disease patients can affect lipid synthesis and metabolism through a variety of metabolic pathways, resulting in significant differences in serum metabolites. Liu *et al.*[138] showed that there were significant differences in TC, HDL, LDL, triacylglycerol, and thyroid stimulating hormone (TSH) between GD patients and HT patients and the normal population, and the distribution of FFAs was similar among the three groups. It may be that the significant increase in lipolysis in white adipose tissue during hyperthyroidism is accompanied by an increase in the uptake of FFAs in oxidized tissues such as liver and muscle. In contrast, in hypothyroidism, decreased lipolysis in white adipose tissue is accompanied by decreased intake of FFAs by the liver. Studies in humans and rodents have found that thyroid hormone affects phospholipid metabolism by modifying phospholipid composition by regulating a variety of enzymes, including desaturase, phospholipase and acyltransferase.[136]

A growing body of literature has revealed differences in gut microbiota composition between patients with thyroid disease and healthy individuals. Zhao *et al.*[139] showed that compared with healthy controls, the microbiome of HT patients had higher richness and diversity. *Firmicutes*/*Bacteroidetes* ratio, used as an indicator of intestinal flora balance, was elevated in HT patients. Similar relationships have been observed in metabolic syndrome and functional gastrointestinal disorders, where gut microbiota has been demonstrated as a key player in pathogenesis.[140] Detailed analysis of the genetic test results of the *16S rRNA* gene showed that the abundance of the groups *Brautella*, *Tella*, *Rumen Streptococcus*, *Bacillus*, and *Eubacter Huotelli* increased in HT patients, while the proportions of *fecalis*, *Bacteroides*, and *Prevotella* were higher in healthy people. Meanwhile, *Bacteroides* can effectively ferments fibers into acetate and propionate. *Bacillus coprofecalis* produces butyrate, which is the main energy source of colon cells and an important epigenetic regulator of immune response.[141]

POTENTIAL THERAPEUTIC APPLICATION

Despite the controversies and unknown mechanism linking the gut microbiota and CNSDs, it is still anticipated that microbial therapies may be beneficial for CNSD in the future. Additionally, microbiota-targeted treatments combined with traditional medications may be more effective than either treatment alone. Nevertheless, study in this field is in its infancy and has numerous limitations and challenges, consequently, further investigations are required.

Faecal microbiota transplantation (FMT) is a method that places stool from a healthy donor into the gastrointestinal tract of another patient, directly changing the recipient's gut microbiota and normalising the composition, thereby providing therapeutic benefits.[142] FMT used to be commonly used for treating gastrointestinal diseases such as ulcerative colitis.[143] Nowadays, FMT is being experimentally used for treating extraintestinal diseases such as autism spectrum disorder, multiple sclerosis, chronic fatigue syndrome, irritable bowel syndrome, and PD, among others. There have been clinical precedents of using FMT to treat CNS disorders. In 2019, Huang reported the first case of using FMT to treat a patient with PD and constipation. The patient's gastrointestinal and neurological symptoms, including constipation and tremors, were effectively reduced after FMT treatment. Furthermore, the study found an increase in *Megamonas* and *Akkermansia* after the FMT treatment.[144] Xue *et al.*[145] reported that FMT could alleviate PD symptoms with acceptable safety, and colonic FMT was preferred over nasointestinal FMT. Live bacteria known as *probiotics* and selectively fermented ingredients called prebiotics can be viable alternatives to clinical FMT. For example, administering Panax notoginsenoside extract prior to

stroke was shown to be neuroprotective in rats by regulating gamma-aminobutyric acid-b (GABA-b) receptors through an increase in *Bifidobacterium longum*.[146] Pre-stroke administration of *probiotics* has also been found to suppress the production of proinflammatory cytokines like TNF-α and Interleukin-6 (IL-6), reduce hippocampal neuronal injury, and restore spatial memory behavior in a mouse model of stroke induced by hypoperfusion.[147] A recent meta-analysis revealed that supplementing enteral nutrition with *probiotics* in stroke patients resulted in lower levels of serum TNF-α, IL-6, and IL-10, as well as a reduced incidence of post-stroke complications such as esophageal reflux, bloating, constipation, diarrhea, gastric retention, and gastrointestinal bleeding.[148]

With the deepening of the research on the relationship between metabolic abnormalities and CVD, clinical studies have confirmed that the level of BCAAs in peripheral blood can be used as a predictive and diagnostic marker for CVD, and once integrated into the existing clinical risk management, it can bring new prevention and treatment methods for CVD. Besides peripheral blood, the preventive, diagnostic and prognostic value of BCAAs levels in other clinical biological samples such as urine and feces remain to be investigated. The use of drugs to regulate myocardial energy metabolism, increase the utilization rate of substrates, and solve the problem of metabolic disorders has great prospects for the improvement of CVDs. However, the research on improving myocardial energy metabolism to treat CVDs by drugs is still in the initial stage, and most of them are experimental studies, and there is a lack of large-scale randomized controlled clinical studies. More clinical studies are needed on the basis of deeper exploration of the potential pathological mechanism of abnormal metabolism of BCAA and abnormal metabolism of glucose and lipid. To explore more drugs to reduce cardiovascular risk and provide real help for the diagnosis, treatment, prognosis and individualized treatment of patients with CVD. Metabolic medicine can comprehensively evaluate endogenous metabolites in the body. Through qualitative and quantitative analysis of all low molecular weight metabolites in the course of a specific disease, it can directly and effectively reflect the small changes in gene and protein expression in the course of disease occurrence. In order to explore the potential targets and metabolic pathways related to the pathogenesis of endocrine disordered diseases such as diabetes, obesity, thyroid disease, and further improve the disease-related pathogenesis, so as to provide diagnostic reference and guide clinical treatment. Since metabolites are participants of metabolic pathways, they could also provide insights into molecular pathways that cause endocrine system diseases.

In conclusion, metabolomics are powerful technologies that can be leveraged to study biomarkers of endocrine system diseases. The integration of metabolomics with genomics and other omics data could help elucidate pathways of disease development and profiling in randomized control trials could provide information on therapeutic effect or response. Significant care, however, must be put into technology choice, study design, sample preparation, and data analysis to obtain informative results. In the future, untargeted methods can drastically expand the pool of circulating biomarkers that can be studied while use of these technologies in therapeutic trials could also identify markers of individual response to therapies. In this way, these technologies can further the clinical treatment as well as scientific understanding of endocrine system diseases.

PROSPECTS AND CHALLENGES

Significant new findings in disease-oriented metabolic research are reported every week, reinforcing the penetration of metabolic analysis into all areas of biology and pathology, making it increasingly possible to reverse disease dysfunction by interfering with metabolic processes, extending from therapeutic medications to dietary changes. However, to date, current research has focused too much on the abnormal reduction of metabolites, known as catabolism, which often represents only a superficial phenomenon. Therefore, the close relationship between macromolecular synthesis, metabolite accumulation, cell signaling, chromatin dynamics, and diseases needs further study.

In addition, the use of metabonomics only measured high flux is small molecular classification, and quantitative is not a metabolic process is complete. Metabolism is a flowing, dynamic process, and static metabolomics cannot reflect this feature of the metabolic process. Metabolic flow technology uses stable isotope tracing technology to analyze the isotope labeling of downstream metabolites to calculate the flow direction and distribution of the compound in the metabolic pathway. By performing metabolic flow analysis on organisms, the activity of specific metabolic pathways in an organism can be obtained. Combined metabolomic-metabolic flow studies, despite technical challenges, are of great value because they provide a quantitative and comprehensive readout of changes in metabolic pathway activity, leading to a deeper understanding of the individuality of metabolism and the biological basis of human disease.

DECLARATION

Author contributions

Ding SS: Writing—Original draft, Writing—Review and

Editing, Visualization, Supervision, Project administration. Wu QT, Lu C, Wang ZM, Lan Y: Investigation, Writing—Original draft. Fang L: Conceptualization. Zheng LM: Conceptualization, Resources, Supervision, Project administration, Funding acquisition.

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