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REVIEW

Metabolic Neurophilosophy: Linking Brain Function with Body Metabolism

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Abstract—This special issue of Biochemistry (Moscow) "Interaction between Neural Signals and Metabolic Pathways: Role in the Functioning of a Healthy and Diseased Brain", includes studies on the mechanisms of close functional connections between the brain and other organs and tissues of the body. These mechanisms link brain metabolism with its signaling function under normal and pathological conditions. The metabolic signals that enable these connections are the focus of research in this field, which is crucial for an integrated understanding of how the body functions. An impairment in metabolic signaling leads to the development of various pathologies. Metabolites such as glucose, fatty acids, and amino acids act as primary signals that influence neural networks and brain chemistry. This connection between the body's metabolism and brain signaling is not merely a matter of fuel supply, but rather a complex information exchange process. The interaction between the brain and the body occurs within the framework of coordinated work of two main axes: the brain-to-body axis ("from top to bottom" or from center to periphery), and the body-to-brain axis (from periphery to center). This relationship between brain function and body metabolism forms a mechanical and logical connection between metabolic somatic diseases and brain disorders that may underlie their comorbidities. The close connection between brain function, metabolism, and the metabolism of peripheral organs and tissues forms the basis for treating "body-brain metabolic" disorders. Identifying the molecular and cellular mechanisms underlying this relationship allows identifying targets for treating and preventing comorbid somatic and brain conditions. The recent achievements, which prove the close relationship between metabolism and brain activity, have led to the emergence of a rapidly growing interdisciplinary field at the interface of neuroscience, philosophy of consciousness, and functional biochemistry of metabolism. This new synthetic field can be called "metabolic neurophilosophy". Its subject is to explore the integrity and inseparability of the body's metabolism (including both in the brain and peripheral organs and tissues) and the signaling and informational function of the brain. It also studies the dependence of all brain activity, including cognition, and mental states on energy processes and metabolic signaling throughout the body.

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INTRODUCTION

"It is clear to all that the animal organism is a highly complex system consisting of an almost infinite series of parts connected both with one another and, as a total complex, with the surrounding world, with which it is in a state of equilibrium. The equilibrium of this system, as of any other system, is a condition for its existence. *And if in certain cases we are unable to disclose the purposeful relations in this system,*

the reason is that we lack knowledge; it does not mean at all that these relations are absent in the system during its continual existence." [1]. This quote from Ivan P. Pavlov's Nobel Prize speech, which he delivered in Stockholm on December 12, 1904, reflects the concept of the body as a complex, self-regulating homeostatic system that is inextricably linked to the environment. The special issue of the Biochemistry (Moscow) "Interaction between Neural Signals and Metabolic Pathways: Role in the Functioning of a Healthy and Diseased Brain" is devoted specifically to the search for "the purposeful relations" at the molecular level between the most important parts of the body as a system – the brain/its structures and peripheral organs/tissues. It is the metabolic signals that realize these connections, therefore, research in this field is the core for an integrative understanding of how the body functions and how a violation of metabolic signaling leads to the development of illnesses, both somatic and brain diseases.

It is routine to distinguish between two functional groups of enzymes and metabolic pathways. Core/housekeeping metabolism includes the processes necessary for the survival of any living cell, such as glycolysis, the Krebs cycle, ATP synthesis, DNA replication, transcription, and protein synthesis by ribosomes. The second group, known as specialized/tissue-specific metabolism, includes processes that are specific to cells of certain tissues. These processes include the synthesis of neurotransmitters in the nervous system, hormones in the endocrine glands, bile acids in the liver, insulin in the pancreas, and contractile metabolism in muscles [2]. This fundamental concept of biology, biochemistry, and molecular biology has been included in textbooks for a long time and is supported by data from proteomics and metabolomics [3, 4]. It is estimated that about 44% of all human genes are expressed in all tissues (housekeeping genes), while the remaining genes have a more specialized function. It is the specialization of organs and their interaction within the body that explains how and why different tissues use metabolic substrates differently. The classical examples from the Lehninger Principles of Biochemistry [2] are: the gluconeogenesis pathway is active in the liver and kidneys, while respective enzymes are present throughout the whole organism; the brain uses glucose primarily for energy production, but the liver also uses it to create glycogen stores and synthesize fats.

It has now become clear that the metabolic specialization of organs serves as the basis for adaptive interactions between neural signals and metabolic pathways throughout the body, and that disruptions in these interactions underlie the development of both cerebral and somatic pathologies. To simplify the consideration of these interactions, we will separate two main levels: the relationship between brain metabolism and its specific functions (intracerebral level), as well as the relationship between the metabolism of peripheral organs and tissues on the one hand and brain activity on the other. The arbitrary nature of this division is evident, since these levels are interconnected, indeed; however, considering them separately allows us to identify the specific patterns of each one.

THE RELATIONSHIP BETWEEN BRAIN METABOLISM AND BRAIN FUNCTIONS

The metabolism of the brain (and the nervous system as a whole) differs significantly from that of peripheral organs and tissues (Fig. 1). First, its energy metabolism is entirely dependent on glucose as a substrate [5]. Only under conditions of glucose deprivation does the brain switch its metabolism to use ketone bodies as energy substrates [6]. Glucose, the brain's primary "fuel," ensures ATP production, the regulation of oxidative stress, and the synthesis of neurotransmitters, neuromodulators, and structural components. Glucose oxidation in neurons exceeds that in astrocytes, but in both cases, oxidation rates increase in direct proportion to excitatory neurotransmission, signal transmission and metabolism being closely linked at the local level [7].

Second, there is the lactate shuttle, a model of which was proposed in 1994 by Pierre Magistretti and Luc Pellerin [8-10]. Neurons specialize in signal transmission and "delegate" part of their metabolism to astrocytes, which absorb glucose from the blood, convert it into lactate, and supply it to neurons that use lactate as a substrate for their mitochondria. Astrocytes possess unique anatomical, morphological, and metabolic features allowing them to absorb substrates from the blood and metabolize them for local delivery to active synapses, thereby supporting neuronal function. The mitochondrial respiratory chain is more "compactly" organized in neurons than in astrocytes, so the bioenergetic efficiency of mitochondria is higher in neurons. Consequently, the production of reactive oxygen species by mitochondrial complex I is very low in neurons and very high in astrocytes, and the naturally high content of reactive oxygen species in astrocytes physiologically determines a specific transcriptional profile that contributes to the maintenance of cognitive functions. The energy and redox metabolism of astrocytes must complement the metabolism of neurons to maintain normal brain function. This is intercellular metabolic specialization within the brain: glucose metabolism is divided between two cell types: astrocytes carry out glycolysis and "stop halfway," producing lactate,

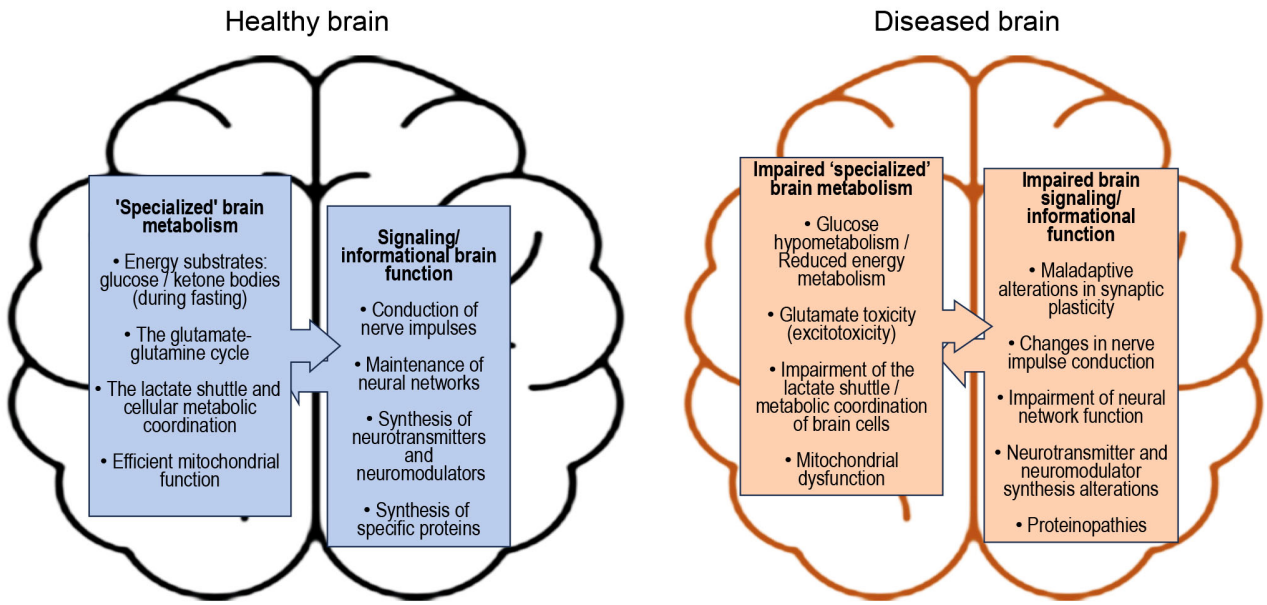

Fig. 1. Brain metabolism and brain signaling function. The diagram illustrates the key components linking brain metabolism and brain function under normal conditions and in pathological states.

while neurons supply this lactate to the Krebs cycle, which allows mitochondria to be involved in the oxidation process. Third, there is the glutamate-glutamine cycle, a specialized process in which neurons release the neurotransmitter glutamate, and astrocytes take it up and convert it into glutamine – a metabolite that is recycled for the synthesis of a new glutamate molecule (this synthesis is a very energy-demanding process) [11, 12].

In brain diseases (including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, etc.), critical metabolic alterations occur in the brain, and as a result the metabolic specialization and cell cooperation are impaired. The key change is a decrease in energy exchange due to glucose hypometabolism. Brain cells lose their ability to efficiently absorb and break down glucose, therefore neurons do not have enough energy to maintain ion pumps and other mechanisms necessary for conducting nerve impulses, which leads to impaired signal transmission, neurodegeneration and neuronal death. Interestingly, hypometabolism is the earliest sign that is noticeable on positron emission tomography (PET) scans 10-15 years before the onset of symptoms of Alzheimer's disease [13]. Another key factor in the development of brain pathologies is an impairment of the lactate shuttle. Metabolic disorders are accompanied by reactive gliosis, astrocytes reduce the metabolic support of neurons, switching to the synthesis of pro-inflammatory molecules. Without metabolic support, neurons become extremely vulnerable to any stress factors. The central event of the hypometabolic state is mitochondrial dysfunction [14, 15]. The processes of mitochondriogenesis and mitophagy do not proceed normally, damaged though functioning mitochondria generate reactive oxygen species, supporting oxidative stress, and electron leakage exacerbates hypometabolism. The glutamate-glutamine cycle is impaired, as astrocytes are unable to effectively take up excess glutamate from the synaptic cleft. The hyperglutamatergic state of neurons promotes excitotoxicity, and the constant influx of calcium ions into hyperexcited neurons triggers programmed cell death [16].

PERIPHERAL TISSUE METABOLISM AND BRAIN FUNCTION

The main links between peripheral tissue metabolism and brain function are shown in the simplest form in Fig. 2. Metabolism is the "language" in which the body informs the brain about available resources. The brain responds by changing its chemical balance (neurotransmitters) and rebuilding its information highways (networks). The metabolism of the brain and the rest of the body are connected through a system of "request and suggestion". The brain does not just consume the resources provided by the body, but actively controls the metabolism of the periphery in order to ensure an uninterrupted supply of energy substrates. Considering these issues, it is routine to analyze separately the axes connecting the brain to a specific peripheral organ: brain-liver, brain-heart, brain-gut, brain-adipose tissue, etc.; occasionally, a third peripheral organ is added to such an axis [17].

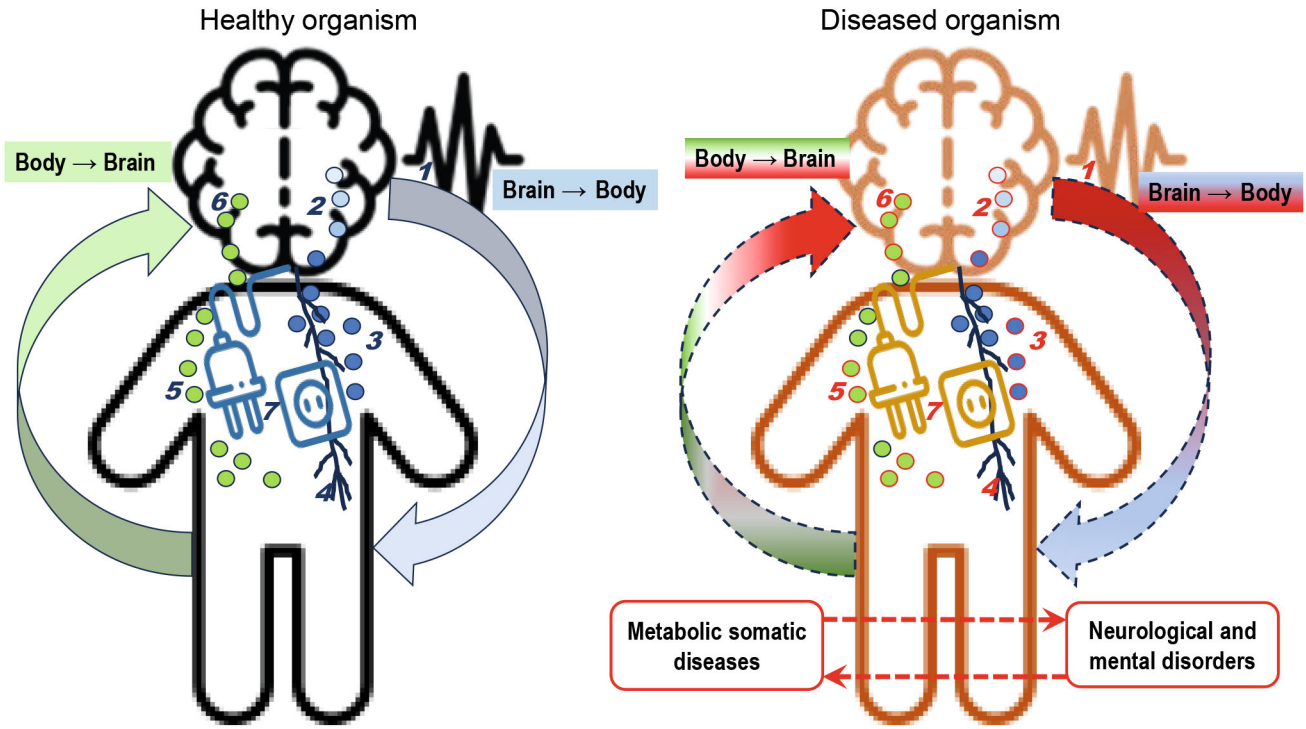

Fig. 2. The interaction between the body's metabolism and the functioning of a healthy or diseased brain is carried out within the framework of the coordinated work of the axes: brain-to-body (from top to bottom, from the center to the periphery) and body-to-brain (from the periphery to the center). *Healthy organism, brain → body.* The specific "electrical" activity of the brain (1) regulates the body's metabolism through several basic mechanisms. As a result of activation of the hypothalamic-pituitary link (2) of neuroendocrine regulation, neurohormones trigger several key neuroendocrine axes (3), including the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid, hypothalamic-pituitary-gonadal, and hypothalamic-prolactin axes. Neurohumoral signals regulate metabolic processes, ensuring the activation of adaptation systems and the maintenance of normal functioning of organs and tissues. By sending electrical and chemical signals to the peripheral nervous system (autonomic and somatic), the brain additionally regulates the body's metabolism, in particular through the sympathetic and parasympathetic parts of the autonomic nervous system (4). *Healthy organism, body → brain.* Certain metabolic products of organs and tissues (5) are able to cross the blood-brain barrier and enter the brain (6), where they can directly interact with neurons and non-neural components. Thus, the brain and the body's metabolism are closely related, given that energy for brain activity (mainly in the form of glucose) is supplied to it from the periphery (7). *Sick organism.* A violation of the above-described interaction occurs in the diseased organism, and changes in any link cause either adaptive or pathological changes in other links. For example, when glucose delivery to the brain is impaired for various reasons (5, 6, 7), the functioning of neurons changes (1), the regulation of the neuroendocrine block (2, 3) and the peripheral nervous system (4) is disturbed, which leads to metabolic changes in the body and disrupts the regulatory functions of the body-brain axis, forming a vicious cycle. This scheme, which combines body metabolism and brain function into a single system, links metabolic somatic diseases (diabetes, obesity, metabolic syndrome, other inherited and acquired metabolic disorders) with neurological and mental brain diseases (including those accompanied by cognitive decline and/or affective disorders).

This is due to the fact that the brain is connected to each peripheral organ by numerous metabolic, nervous and neurohumoral connections, and consideration of the interrelationships of many organs all together is possible only at the most general level, without relevant specific details discussed for simple peripheral organ-brain axes.

The human brain makes up 2% of the body weight, but consumes about 20% of the body's energy. Nevertheless, it is more energy efficient than most computers [18]. According to the "Selfish Brain Theory" proposed by Achim Peters, when resources are scarce, the brain prioritizes itself by limiting glucose supply to the rest of the body through several mechanisms [19-21]. The brain, through the sympathetic nervous system, suppresses insulin secretion and stimulates the release of cortisol; as a result, muscles and adipose tissue enter a state of temporary "insulin resistance", leaving glucose available in the blood for the needs of neurons. The effects of the brain on the liver, which are induced, for example, by fasting, are aimed at increasing blood glucose levels: activation of glycogenolysis and gluconeogenesis, as well as ketogenesis as an opportunity for the brain to use fatty

acid energy. The brain is considered as a dispatcher that controls the body's metabolism in order to constantly receive its 20% of the total energy of the body, even at the expense of depletion of peripheral organs and tissues.

The integration of body and brain is realized by functioning of neurohumoral systems (Fig. 2). The brain effectively controls the body through the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, but in pathological situations these commands become destructive. HPA axis is the main interface that translates the "chemical" language of metabolism into the "electrical/digital" language of neural signals and *vice versa*. It promotes conversion of energy resources (glucose, fat) into behavioral strategies (fight, flight, search for food). HPA hormones glucocorticoids (GCs, cortisol in humans, corticosterone in rodents) play the role of a metabolic manager that effectively redistributes energy flows between the body and the brain [22]. Realizing the priority of the brain, when HPA axis is activated, cortisol causes temporary insulin resistance in muscles and adipose tissue. This keeps glucose in the bloodstream, making it available to the brain. Cortisol stimulates gluconeogenesis in the liver, ensuring the availability of fuel for the high-cost signaling function of neurons even during starvation. GCs make a significant contribution to the association between metabolism and the specific informational function of the brain. HPA axis modulates specific informational processes in the brain through glucocorticoid and mineralocorticoid receptors in the hippocampus and prefrontal cortex [23, 24]. Moderate release of GCs enhances long-term potentiation (LTP) – the cellular mechanism of memory, directing metabolic energy to memorize information important for adaptation. Chronic activation of HPA axis in metabolic disorders (for example, in obesity) causes dendritic atrophy, negatively affecting cognitive function [25].

Feedback from peripheral organs and tissues to the brain is also realized at the HPA level; this key neurohumoral system not only mediates the "orders of the brain", but also perceives body information through specific sensors. Signaling molecules for "informing" the brain about the state of energy depots are metabolic hormones, for example, the hormone of adipose tissue leptin and the hormone of the stomach ghrelin. When hormonal connections are impaired (for example, in obesity), leptin resistance develops. The brain interprets a decrease in leptin signaling as an indication that the body is starving, although there is an excess of fat, and begins to regulate metabolism in the direction of slowing down. The main mechanism of these phenomena is that leptin and ghrelin directly modulate hypothalamic activity, suppressing or enhancing the stress response [26, 27]. If the body signals starvation (high ghrelin), HPA axis is activated, stimulating the appropriate processes in the brain. Glucosensing neurons, specialized brain cells, primarily located in the hypothalamus, arcuate nucleus and hindbrain, monitor glucose levels and regulate energy homeostasis by altering their firing rates. A drop in blood sugar is a direct signal for HPA axis to trigger a stress response (release of adrenaline and GCs) [28]. HPA axis regulates the switching between brain networks, integrating the body and brain and converting the metabolic status (hunger/satiety/inflammation) into a psychophysiological state (anxiety/tranquility/attention).

Chronic stress transforms HPA axis from a protective mechanism into a pathological one due to an allostatic load, making the cost of adaptation too high for brain [29]. This situation is associated with the impairment of the normal connections between body metabolism and brain function. Chronically elevated GCs significantly impair neuronal energetics. Normally, GCs provide the energy substrate for the brain, but under chronic stress, they inhibit glucose transport through the GLUT3 glucose transporter in neurons. As a result, in spite of high blood glucose levels, brain cells cannot absorb and use it, which leads to energy deficiency and loss of specific functions (for example, synthesis of complex neurotransmitters) [30]. Normally, astrocytes supply neurons with lactate, but chronic stress impairs their metabolism. GCs inhibit the expression of glutamate transporters in astrocytes, glutamate accumulates in the synaptic cleft and a hyperglutamatergic state of neurons develops [16, 31]. Chronic activation of HPA axis also affects the mitochondria, the central link of cellular energy metabolism. Excessive GCs increase electron leakage in mitochondria, causing the generation of free radicals, oxidative stress, and damage to mitochondrial membranes and mitochondrial DNA [32]. Cortisol directly suppresses the activity of telomerase, an enzyme that protects the ends of chromosomes [33]. Excess GCs also inhibits neurogenesis (especially in the subgranular neurogenic niche of the hippocampus) inducing impairment of brain plasticity [34].

Thus, the connection between the body metabolism and the brain signaling systems is not just a "fuel supply", but a complex informational exchange. Metabolites (glucose, fatty acids, amino acids) act as primary signals that retune neural networks and brain chemistry. Many neurotransmitters are synthesized directly from precursors that come from food, so the status of the body metabolism determines their availability. For example, the level of serotonin in the brain depends on the transport of tryptophan through the blood-brain barrier, and insulin facilitates this transport [35]. The main excitatory (glutamate) and

inhibitory (GABA) mediators are directly related to the Krebs cycle. Under metabolic stress (ketosis), the balance shifts towards GABA, which has an inhibitory and anticonvulsant effect [36]. The dopaminergic system controls glucose and lipid metabolism through several mechanisms at the central level (including appetite control and decision-making), regulating body weight and energy metabolism [37, 38]. In the pituitary gland, dopamine inhibits prolactin production and stimulates insulin secretion through dopamine receptor 2. In addition, it can affect various physiological components of the peripheral system, such as pancreatic beta cells, adipocytes, hepatocytes, and muscles, regulating secretion of insulin, glucagon and glucagon-like peptide-1, glucose uptake and utilization, and fatty acid metabolism. An important link in the metabolic effects of dopamine is the dopamine-aminotransferase system [39]. Metabolic disorders (obesity, insulin resistance) are associated with the decrease in the sensitivity of dopamine receptors [40].

On the other hand, as mentioned above with regard to both leptin and ghrelin, metabolic hormones also perform the functions of neuromodulators: hormones that regulate metabolism in the body have receptors in key brain structures (hypothalamus, hippocampus, cortex) [41]. So, in the brain, insulin works not only as a glucose regulator, but also as a signal of synaptic plasticity. The body's insulin resistance "deafens" synapses, preventing them from changing the strength of the neural connections that underlie learning [42]. Leptin and ghrelin modulate the dopamine reward system and glutamatergic transmission in the hippocampus, directly affecting cognitive abilities and decision-making [43]. It is also important that ATP, the main currency of metabolism, works in the nervous system as a neurotransmitter through purinergic receptors. When the body's metabolism is impaired, the release of ATP by microglial cells can trigger a cascade of inflammation, altering the signaling activity of entire brain regions [44].

The default operational definition of neural information processing is that it is ultimately encoded as a change in the firing frequency of individual neurons, since this correlates with the presentation of a peripheral stimulus, motor action, or cognitive task. It is believed that the metabolic energy that supports the background activity correlates with differences in the frequency of neuronal firing. Based on these concepts, the principles of neuroimaging studies were developed, in particular, the method of functional magnetic resonance imaging (fMRI), which are based on changes in blood oxygen content as an indirect indicator of neural activity. Conceptual frameworks for fMRI neuroimaging paradigms have been developed to explore how current neural activity is related to metabolism [45]. It has been shown that the metabolic state of the body changes the functional connectivity of the brain, directly affecting the interaction of neural networks. With a high level of systemic inflammation (e.g., metabolic syndrome), connectivity in the "default mode network" (DMN) decreases, leading to cognitive deficits. Ketosis and intermittent fasting increase the "metabolic flexibility" of neurons, strengthening the connection between the prefrontal cortex and the limbic system [45, 46]. The use of magnetic resonance imaging in this field of research is very promising, as it allows for an individual assessment of both the level of fMRI and the concentration of key metabolites (choline, N-acetylaspartate, creatine, lactate, lipids, alanine, glutamine and glutamate, GABA, myo-inositol) using the method of magnetic resonance spectroscopy. In this special issue, Korotkov et al. [47] describe a new approach to simultaneous noninvasive individual assessment of functional connections between brain regions and levels of metabolites in the human brain allowing to track the relationship between these indices in different functional states.

THE TRANSLATIONAL IMPLICATIONS OF THE INEXTRICABLE RELATIONSHIP BETWEEN BRAIN FUNCTION AND BODY METABOLISM

Energy homeostasis is achieved by the coordinated action of metabolic organs. The peripheral nervous system innervates the organs and, along with the neurohumoral system, connects them to the brain and plays a vital role in the control of energy homeostasis [48]. Maintaining energy/metabolic homeostasis, providing sufficient energy and essential nutrients, is implemented by a complex system consisting of redundant pathways that normally guarantee the stability of this system. Nevertheless, both the functioning of the brain-to-body axis and the body-to-brain axis can be impaired, and such disorders underlie somatic diseases, brain diseases and their comorbidities. Patterns of interaction between brain regions involved in cognitive, emotional, and metabolic regulatory functions may explain why and how many predisposed people in the modern environment have impaired mechanisms that determine neural appetite control and energy balance regulation. The brain controls the internal milieu through hormonal and neural mechanisms that perceive nutrients. It is constantly influenced by the external environment and lifestyle, which affect the areas of the brain responsible for cognitive functions and emotions through sensory input. These two streams of information are integrated to generate adaptive behavioral (food intake)

and autonomic/endocrine responses that determine nutrient distribution, energy expenditure, and overall energy balance [49]. Any of the peripheral and central signaling stages is susceptible to individual predisposition due to genetic, epigenetic, or non-genetic mechanisms of imprinting at an early age.

On the other hand, impairments of body metabolism associated with peripheral organs inevitably affect the functioning of the brain, since it is the most "demanding consumer" of energy supplied by all organs. Any failure in the supply of metabolites from the outside or other changes in the chemical composition of the blood immediately affect the neurochemistry of the brain and, consequently, its function. In the last decade, there has been a growing interest in understanding how changes in metabolic functions lead to an increased risk of diseases, including diseases of the nervous system [50, 51], and the number of studies on the complex relationships between brain function and "metabolic health" is growing exponentially. Currently, several key universal signaling mechanisms from the periphery to the brain are being considered, the failure of these pathways potentially resulting in brain pathology.

In metabolic disorders (e.g., obesity or type 2 diabetes), adipose tissue begins to release pro-inflammatory cytokines, initiating the development of systemic inflammation. Even with low-level systemic inflammation, cytokines, penetrating through the blood-brain barrier, activate microglia in the brain, which leads to neuroinflammation impairing synaptic plasticity [52, 53]. Metabolic disorders are also associated with systemic insulin resistance, which is associated with insulin resistance in the brain. Insulin in the brain is involved not only in glucose metabolism, but is also a signaling molecule involved in memory and learning mechanisms; insulin resistance impairs the functioning of the hippocampus responsible for memory formation [54, 55]. Cognitive functions are most dramatically impaired in patients with poorer glycemic control; with increasing duration of diabetes, the rate of cognitive decline accelerates and the risk of dementia increases significantly [56].

Lipid metabolism disorders affect the state of the vascular wall and are involved in the development of microangiopathies and subsequent vascular dementia associated with insufficient supply of glucose and oxygen to neurons and neurodegeneration [57, 58]. Disorders of the detoxification function of the liver or kidneys and the accumulation of body metabolic products as a result directly affect brain function (hepatic and renal encephalopathies) [59, 60]. For example, in liver diseases, the level of ammonia in the blood increases (hyperammonemia), which easily passes into the brain and is neutralized by astrocytes, turning into glutamine. Excess glutamine causes astrocyte swelling, which is the main cause of brain edema and subsequent impairment of neuronal function [61, 62].

Metabolic disorders are frequently accompanied by intestinal dysbiosis. Bacteria produce up to 90% of serotonin and short-chain fatty acids (SCFA), which are critically important for the integrity of the blood-brain barrier. As a result, a "leaky gut" is often associated with a "leaky brain", allowing toxins, that normally should have been filtered out, to enter neurons [63, 64]. Currently, impaired functioning of the gut-brain axis has been documented in almost all somatic and brain diseases studied in this regard, including neurodegenerative and psychiatric disorders [65, 66].

At present, there is an obvious trend towards taking into account metabolic disorders when considering the pathogenesis of neurological diseases, up to the consideration of some of them (e.g., Alzheimer's disease) as a metabolic disease [67-69]. A number of researchers approach the substantiation of the "metabolic theory of mental health". Based on the numerous data obtained in the clinic and experiment, it is proposed to consider mental disorders (including schizophrenia, depressive disorders) as metabolic diseases of the brain [70-73]. Christopher M. Palmer has summarized abundant evidence that mental illnesses (from depression to schizophrenia) are actually metabolic disorders of the brain associated with mitochondrial dysfunction [74]. It is possible to discuss metabolic disorders in various brain diseases as a mechanistic basis for their development or as comorbid somatic pathologies. The search for metabolic targets for the treatment of mental disorders is recognized as an imperative approach to the treatment of these conditions [75], and the use of appropriate diets that correct metabolism is considered as one of the actual possibilities of therapy [76].

Metabolic disorders occupy a special niche in the development of various forms of epilepsy. More than 600 different metabolic disorders can lead to a clinical picture in which seizures are the main neurological manifestation, either as a primary clinical picture or as part of a more complex phenotype. The term "metabolic epilepsy" is commonly used to refer to these metabolic disorders, many of which are associated with mutations in genes related to metabolism [77]. Symptomatic (structural) epilepsy can cause metabolic disorders, and those in turn can induce epilepsy, forming a bidirectional pathological cycle. Over the past century, since the very beginning of the use of ketogenic diets for the treatment of epilepsy, it has been confirmed that metabolic interventions can control seizures. For example, metabolic disorders such as impaired glucose levels and vitamin B6 deficiency can directly cause epilepsy, while epileptic

seizures themselves can cause lactic acidosis, electrolyte imbalance, and other unfavorable changes of internal milieu [78]. Impairments of lactate metabolism not only contribute to the pathogenesis of epilepsy due to acidification of the microenvironment, but also affect neuroinflammation, imbalance of energy metabolism, dysregulation of neurotransmitters, synaptic plasticity and epigenetic regulation through lactylation, a newly discovered posttranslational modification that regulates protein functions and gene expression by covalently attaching lactate groups to lysine residues [79]. Numerous data highlight the critical role of neuroinflammation and metabolism interaction in the pathophysiology of epilepsy. Metabolic dysregulation and neuroinflammation exacerbate each other, creating a vicious circle associated with pathologically altered metabolism of glucose, glutamate/GABA, tryptophan, kynurenine, adenosine, and lipids [80, 81]. Metabolic disorders are also associated with the development of pharmacoresistant epilepsies, primarily through changes in the metabolic pathways of alanine, aspartate, and glutamate, as well as the biosynthetic pathways of phenylalanine, tyrosine, and tryptophan [82]. These metabolites can be used as prognostic biomarkers of pharmacoresistant epilepsy and potential therapeutic targets for the development of new drugs. It has been shown that astrocytes are not only involved in the regulation of the metabolism of neural networks, but are also closely associated with the development of neuroinflammation, a vital factor associated with the progress of pharmacoresistant epilepsy [83]. Metabolic reprogramming of astrocytes and microglia initiates epileptogenesis, due to the hyperexcitability of neural networks, neuroinflammation and oxidative stress. Key mechanisms of glial dysfunction include a shift to aerobic glycolysis (the Warburg effect), mitochondrial disorders, and generation of reactive oxygen species [84]. These processes are regulated by the Wnt/GSK3b and mTOR signaling pathways and eventually form a vicious circle of energy deficiency, NLRP3-inflammasome activation, and excitotoxicity.

Hans Selye regularly stressed the need for a holistic approach when considering the processes occurring in the body: “No matter how much we learn about the intimate mechanisms of biological phenomena, we shall always have to use the old-fashioned holistic approach which looks at the living organism as a complex highly organized system and not as a mere sum of its parts.” [87]. Remarkably, Selye’s opinion largely coincides with the quotation from Pavlov’s Nobel Prize speech in 1904 given in the Introduction [1]. The data obtained in recent decades on the close metabolic and neural connections between organs as the basis of the body’s existence have made this “old-fashioned holistic approach” relevant again and, to a certain extent, it became a trend in fundamental medicine, neuroscience and physiology. The original meaning of the Latin phrase “In a healthy body, a healthy mind” (Latin: *Mens sana in corpore sano*), which dates back to a Juvenal’s satire, was an appeal to the gods to send down both a healthy body and a healthy mind. In its modern meaning, this expression as a slogan of preventive medicine and the thesis of the relationship between physical and mental health was consolidated thanks to the philosopher and physician John Locke, who, paraphrasing the ancient source, used this postulate to emphasize the importance of a healthy lifestyle. The organism is an integrated metabolic network. It is almost impossible to treat brain pathologies in isolation from the body’s metabolism (and *vice versa*). To break the vicious circle, modern medicine increasingly suggests “treating the brain through the body”: normalize insulin, activate muscles through physical exercises, and periodically switch the liver to ketone production. The established intimate relationship of brain function and metabolism with the metabolism of peripheral organs and tissues is the fundamental basis for the treatment of “from body metabolism to brain”, while the revealed molecular and cellular mechanisms of this relationship make it possible to identify targets for the treatment and prevention of comorbid somatic and brain diseases. Such targets can be quite specific or, conversely, universal, such as, for example, a neurotrophic factor from the brain, BDNF, a “metabotrophin” that links the signaling function of neurons and systemic metabolism [85, 86].

CONCLUSION. NEUROPHILOSOPHY OF METABOLISM

Thus, the metabolic connection between the brain and the body works both ways. If it was previously believed that the brain is only a passive consumer of the body’s energy substrates, modern research shows that the metabolic connections between the brain and peripheral organs unite the brain and body so closely that brain disease “rewires” the metabolism of the whole organism, and somatic metabolic diseases impairs the functioning of the brain.

Cognitive abilities and behavior are emergent properties of brain systems that pursue to maximize complex and adaptive behavior with minimal energy use, while the human brain’s ability to adaptively predict, process complex information, and act on it is associated with a significant energy load [88]. Numerous studies conducted both on models and on large cohorts of patients confirm the above-mentioned “Selfish Brain Theory”, which considers the brain as an independently self-regulating organ that occupies

a primary position in a hierarchically organized energy metabolism. The theory postulates the vital ability of the brain to prioritize its own energy metabolism and is confirmed in clinical studies [89-91]. Basic brain functions, such as the formation of long-term memory, increase the metabolic activity of stimulated neurons to meet energy needs related to brain function. An evolutionarily (from insects to mammals) conserved mechanism controls mitochondrial metabolism in neurons, participating in the establishment of higher brain functions such as memory [92]. The role of cellular metabolism in learning and memory is currently beyond doubt. When considering the molecular mechanisms of learning and memory, it was suggested that it is the study of neuronal metabolism that is necessary to understand how the internal predictive activity of neurons forms a new learning event [93]. Apparently, the predicted metabolic changes in the brain can also occur in non-neuronal cells, including peripheral tissues.

The philosophy of consciousness dates back to antiquity; the subject of this section of philosophy is primarily the nature of consciousness, as well as the relationship between consciousness and physical reality (the body). As a biological basis, the philosophy of consciousness focused mainly on information processing (neural and/or network activity). Neurophilosophy, or philosophy of neuroscience, is an interdisciplinary study combining neuroscience and philosophy that examines the relevance of neuroscience research to issues traditionally related to the philosophy of mind. With the rapid development of neuroscience, we are increasingly confronted with neurobiological data that address ancient philosophical questions about consciousness and its relationship to the brain. The term neurophilosophy was introduced in 1986 by Patricia Churchland as a unified science of the mind-brain [94, 95]. Neurophilosophy (philosophy of neuroscience) attempts to interpret neurobiological approaches and results using the conceptual rigor and methods of philosophy of science.

Due to achievements of recent years, which show a close relationship between metabolism and brain activity, we are witnessing now the birth of a new synthetic science, which can be called “metabolic neurophilosophy.” This name reflects the essence of a rapidly developing interdisciplinary field at the intersection of neuroscience, philosophy of consciousness and biochemistry of metabolism. This field declares that brain functions, cognition, and mental states are fundamentally dependent on metabolic processes and energy availability, and emphasizes the important role of cognitive and affective functions in the body’s energy supply, nutrients, and metabolic signaling between peripheral organs and tissues and the brain. Metabolism is considered not just as a combination of chemical processes, but as the fundamental basis of life, the psyche, and even subjective experience.

Bruce McEwen, a leading researcher on stress, has shown that the brain, including its higher cognitive centers, is a target of stress and a key organ for responding to stressors. It is true both in terms of perceiving what causes stress and in terms of brain’s ability to determine the effects of stress on both the brain and the body with the help of neuroendocrine, autonomic, immune and metabolic systems [29]. These systems, in turn, ensure either successful adaptation or the development of pathologies due to the combined burden of adaptation to stress and a maladaptive lifestyle – the “allostatic load”. McEwen suggested that plasticity of the brain and its structures (hippocampus, amygdala, prefrontal cortex) underlie learning, memory, and behavior. The features of changes in neuroplasticity in the process of biological consolidation of experience throughout life determine whether events in the social and physical environment will lead to successful adaptation or to maladaptation and mental and physical health disorders. In particular, it follows from this concept that the results of brain functioning (including our thoughts) are metabolic events that shape our physical health. If the term “metabolic neurophilosophy” is adopted, the textbook on this discipline will indicate that the metabolism of the body (including brain and peripheral organs/tissues) and the signaling/information functions of the brain are inseparable. The cognitive process, emotions, and thoughts are not only “programs”, but also an energy – consuming physiological process that shapes the body.

Abbreviations

GCs	glucocorticoids
fMRI	functional magnetic resonance imaging
HPA	hypothalamic-pituitary-adrenal

Contributions

Natalia Gulyaeva developed the concept, carried out the search and analysis of literature data, wrote and edited the manuscript.

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Ethics approval and consent to participate

This work does not contain any studies involving human and animal subjects.

Conflict of interest

The author of this work declares that she has no conflicts of interest.

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