Microglia-Specific Metabolic Changes in Neurodegeneration

Blanca I. Aldana

Department of Drug Design and Pharmacology, *Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark*

Correspondence to Blanca I. Aldana: *blanca.aldana@sund.ku.dk*
https://doi.org/10.1016/j.jmb.2019.03.006
Edited by Kristine Karla Freude

Abstract

The high energetic demand of the brain deems this organ rather sensitive to changes in energy supply. Therefore, even minor alterations in energy metabolism may underlie detrimental disturbances in brain function, contributing to the generation and progression of neurodegenerative diseases. Considerable evidence supports the key role of deficits in cerebral energy metabolism, particularly hypometabolism of glucose and mitochondrial dysfunction, in the pathophysiology of brain disorders. Major breakthroughs in the field of bioenergetics and neurodegeneration have been achieved through the use of *in vitro* and *in vivo* models of disease as well as sophisticated neuroimaging techniques in patients, yet these have been mainly focused on neuron and astrocyte function. Remarkably, the subcellular metabolic mechanisms linked to neurodegeneration that operate in other crucial brain cell types such as microglia have remain obscured, although they are beginning to be unraveled. Microglia, the brain-resident immune sentinels, perform a diverse range of functions that require a high-energy expenditure, namely, their role in brain development, maintenance of the neural environment, response to injury and infection, and activation of repair programs. Interestingly, another key mechanism underlying several neurodegenerative diseases is neuroinflammation, which can be associated with chronic microglia activation. Considering that many brain disorders are accompanied by changes in brain energy metabolism and sustained inflammation, and that energy metabolism has a strong influence on the inflammatory responses of microglia, the emerging significance of microglial energy metabolism in neurodegeneration is highlighted in this review.

Introduction

The multifaceted functions of the central nervous system (CNS) require a healthy microenvironment for brain cells to thrive. The maintenance of such milieu critically depends on microglia, the CNS innate immune cells [1,2]. Microglia are among the most versatile cells in the human body, as they elicit diverse actions critical for the development and homeostasis of the brain. Upon detection of injury or infection, microglia undergo morphological and functional transformations, and rapidly respond to overcome brain insults. This response is known as microglial activation and involves patterned actions including migration to the site of injury and release of immune response molecules such as cytokines, proteases, and reactive oxygen species (ROS) [1,3–5]. Evidence indicates that depending on their activation profile, microglia can promote neuronal survival or lead to neuronal degeneration [3,6–8]. Furthermore, either a sustained or a deficient microglia-derived inflammatory response can be detrimental to the brain. Given the vital role of microglia in normal CNS function, it is not surprising that several brain disorders are associated with microglia dysfunction. In line with this, exacerbated microglia activation has been implicated in neurodegenerative diseases, and it has been suggested that microglia-dependent neuroinflammation may contribute to neurodegeneration [6,9,10]; the specific underlying mechanisms, however, remain elusive.

It is well established that the brain is an energetically expensive organ. The majority of the fuel supply for the brain is utilized to meet the high-

energy requirement associated with synaptic activity [11]. However, experimental evidence indicates that an important fraction of the energy consumption in the brain is not directly related to information processing. Although little is known regarding the brain functions that are so energetically costly, it has been suggested that microglia surveillance and activation could place a considerable strain on the energy budget [12]. Interestingly, impairments in energy processing have been strongly linked to hampered brain function and neurodegeneration [13–15]. Specifically, decreased metabolism of glucose, the obligatory energy substrate in the brain, is widely accepted as an early hallmark in neurodegenerative diseases [16–18].

Another well-recognized factor contributing to the progression of neurodegenerative disorders is neuroinflammation [19], where the exacerbated inflammatory response in the brain is predominantly attributed to microglia. Whether microglia activation is a cause or an effect of disease-associated neurodegeneration is currently under intense scrutiny and debate. Specific mechanisms by which microglia contributes to inflammation-induced neurodegeneration remain elusive, as well as the effects of altered energy metabolism on microglial inflammatory responses. This might be due to the paucity of suitable models to investigate microglia function and the challenging translation of animal models to humans. Moreover, *in vitro* studies of microglial activation should be interpreted with caution, as the microglia phenotype is highly dependent on the particular microenvironment within the CNS. The present review gathers the still limited knowledge regarding the link between alterations in the energy metabolic profile of microglia and disease mechanisms in neurodegenerative disorders. In addition, the therapeutic potential of regulating microglial energy metabolism is focused upon.

Microglia, More Than Immune Surveillance Cells

Microglia account for 10%–15% of non-neural cells in the brain. They are generally described as brain-resident immune cells which closely resemble peripheral macrophages [1]. Several homeostatic functions in the CNS can be ascribed to these highly dynamic cells [20,21]. Among these, microglia are indispensable for normal brain development, participating in synapse pruning, neuronal survival and synaptogenesis [22]. Relevant to their role as immune sentinels, microglia express several immune molecules, including integrins, toll-like receptors, and triggering receptor expressed on myeloid cells (TREM). Furthermore, microglia phagocytize cells and cell debris as well as participate in remodeling of the extracellular matrix [7,23–29]. In line with this, microglia can acquire an ameboid morphology that is associated with increased phagocytosis. Microglia display remarkable plasticity and are capable of responding to a vast array of challenges [20]. Microglia activation in response to infection and tissue damage involves specific morphofunctional changes and represents a first-line innate response. Conversely, chronic microglia activation, particularly the cytotoxic action, has been shown to have negative outcomes in conditions such as stroke and neurodegenerative disorders [6,30–34]. For instance, activation of microglia has been implicated in the inflammatory alterations observed in severe neurodegenerative disease such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [8,19]. Moreover, in such conditions, microglia are believed to act as effectors in the neuronal degeneration. Whether protective or harmful, microglial perpetual state of motion continuously scanning the CNS imposes a large-energy requirement (Fig. 1) [12].

Brain Energy Metabolism in a Nutshell

Brain activity requires a large and continuous energy supply. About 25% of glucose and 20% of the oxygen consumed by the body are directed to support cerebral function, although the brain represents only 2% of the total body weight [11,35]. The main processes contributing to the high brain energy demand include restoration and maintenance of the ion gradients dissipated by signaling processes such as action potentials, as well as neurotransmitter turnover [11,35,36]. While glucose is the main energy substrate of the adult brain, under certain conditions such as development, starvation, and during intense exercise, the brain is capable of utilizing additional energy substrates, such as lactate [37,38] or ketone bodies [39] As in any other cell type, glucose can enter cells via specific glucose transporters (GLUTs). Once in the cytosol, glucose is phosphorylated by hexokinase to produce glucose-6-phosphate (G6P), which can be processed into several metabolic pathways. G6P can be metabolized through glycolysis which gives rise to two molecules of pyruvate, energy in the form of ATP and reducing equivalents as nicotinamide adenine dinucleotide (NADH). Alternatively, G6P can be processed in the pentose phosphate pathway (PPP) subsequently leading to production of reducing equivalents (NADPH). In PPP, G6P is converted into ribulose 5-phosphate utilizing two molecules of NAD^+. Thus, when ample amount of energy is required, the level of NADPH is reduced and the pathway is activated to generate more reducing equivalents. In astrocytes, G6P can be further used for the synthesis of glycogen. Furthermore, several metabolic intermediates produced in the brain from

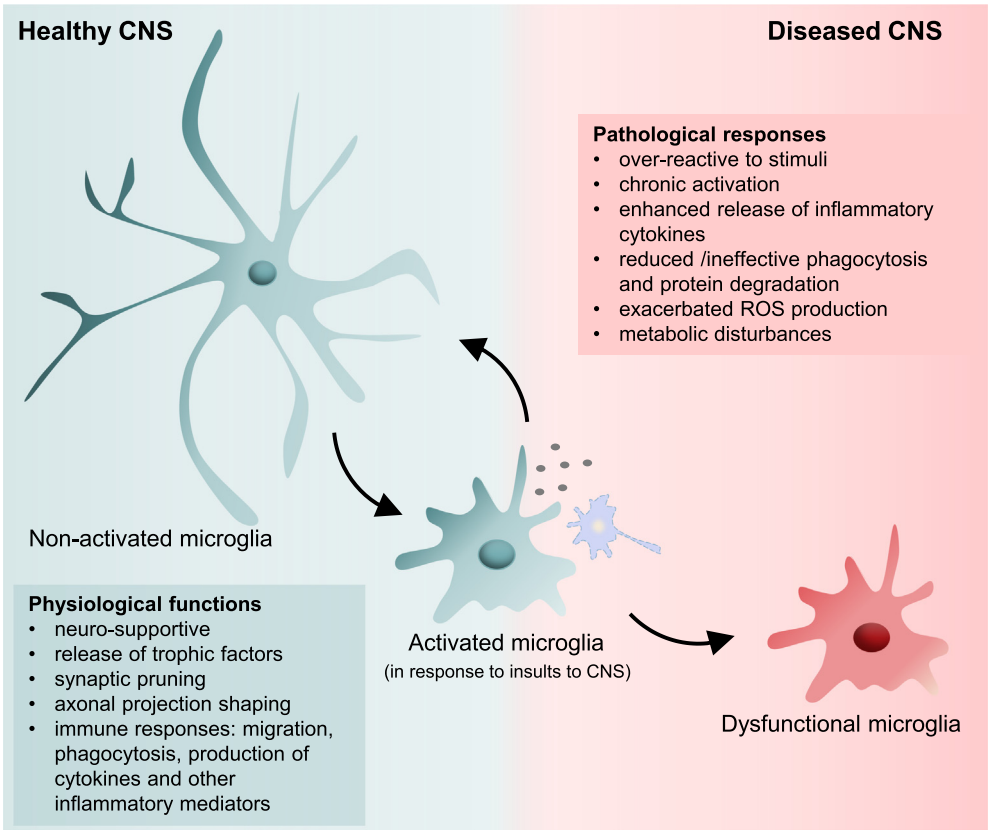

Fig. 1. Microglia, more than immune surveillance cells. Microglia functions may represent a "double-edged sword." These cells are indispensable for normal CNS development and are capable of monitoring the brain environment for clearance of harmful agents and dysfunctional cells. Conversely, during disease progression, microglia then turn into a dysfunctional phenotype which ultimately becomes deleterious.

glucose can subsequently be oxidized for energy production (e.g., lactate, pyruvate, glutamate, or acetate) [40]. Pyruvate can additionally be precursor for lactate synthesis by the enzyme lactate dehydrogenase (LDH). Lactate is mainly released into the extracellular space via monocarboxylate transporters (MCTs). Under aerobic conditions, pyruvate can then enter mitochondria where it undergoes oxidative decarboxylation to produce acetyl-Coenzyme A (acetyl-CoA) and be further metabolized in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, consuming oxygen and further producing ATP and CO_2. In the TCA cycle, the reducing equivalents flavin adenine dinucleotide (FADH2) and NADH are further produced and transfer their electrons (and protons) to molecular oxygen via mitochondrial electron transport chain (ETC) located in the inner mitochondrial membrane. The ETC comprises four enzyme complexes (I–IV), and the transfer of electrons through these complexes is accomplished by co-enzymes ubiquinone and cytochrome C. During this process, protons are transported across the inner mitochondrial membrane from the matrix to the intermembrane space to generate an electrochemical gradient. The ATP synthase (complex V) harnesses the energy from the protons moving down its electrochemical gradient to catalyze the phosphorylation of ADP, thereby generating ATP. The complete oxidation of glucose in the mitochondria produces larger amounts of energy in the form of ATP (30–34 ATP molecules) compared to glycolysis (2 ATP). Mitochondria are major metabolic centers for ATP production in brain cells, and they are crucially involved in amino acid metabolism, oxygen metabolism, ROS production, and calcium handling and are thus critical to cell viability. In addition, mitochondria are regulators of cell death, a key feature of neurodegeneration. Several lines of evidence demonstrate that mitochondria have a central role in ageing-related neurodegenerative diseases [41]. Moreover, a large number of disease-specific proteins interact with mitochondria. Thus, targeting mitochondrial processes, including energy metabolism, ROS generation, as well as abnormal protein interactions with mitochondria, holds great therapeutic potential.

Microglia Energy Metabolism

Microglial survival and function depends on sufficient energy supply [42]. Microglia constantly

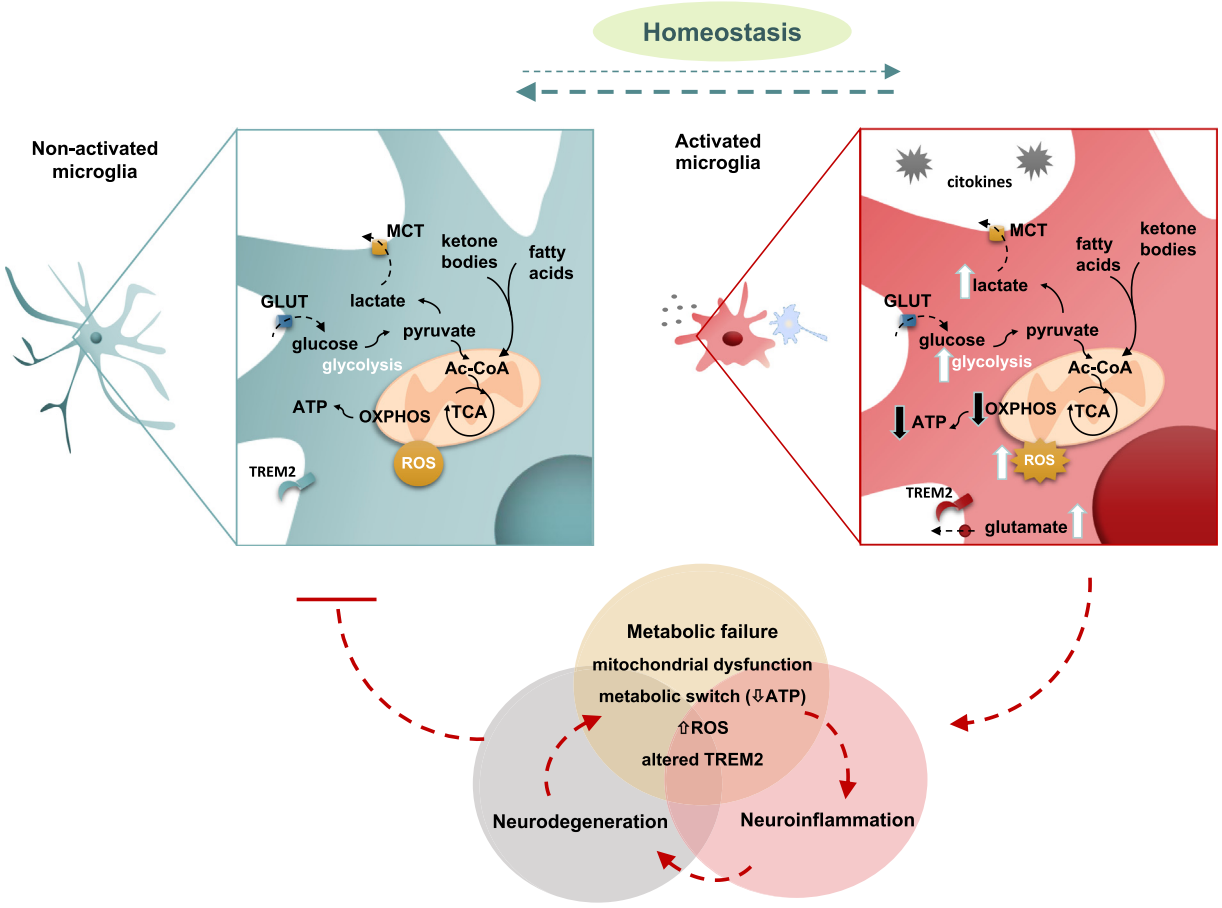

Fig. 2. Possible metabolic switch during microglia activation and the vicious cycle of sustained microglial activation, neuroinflammation, and neurodegeneration. In the healthy adult brain, microglia are mostly in a "resting" state displaying distinct morphological traits including a small soma and ramified morphology with dynamic processes used to monitor the microenvironment. In response to insults, microglia rapidly become activated and reorganize their structure and functions toward protection and repair responses. Microglial activation has been suggested to be associated with a metabolic switch in favor of glycolysis and decreased oxidative phosphorylation (OXPHOS). The acute microglial neuroinflammatory responses involve release of several inflammatory mediators such as cytokines and may trigger oxidative stress (ROS). This acute response is thought to be beneficial to the CNS, as it can prevent further neuronal damage and promote repair mechanisms. In contrast, chronic neuroinflammation may be detrimental because once activated, microglia can release potentially harmful factors that may stimulate the activation of additional microglial cells in a self-renewing damaging cascade. Under these conditions, mitochondria are a particularly vulnerable target of oxidative stress and proinflammatory mediators that may damage essential mitochondrial components such as enzymes of the ETC and mtDNA. Simultaneously, a primary mitochondrial dysfunction accompanied by elevated ROS production could induce microglial activation. Interestingly, microglial activation and mitochondrial dysfunction have been proposed to trigger and perpetuate molecular pathways leading to neuronal degeneration.

move their processes through the brain parenchyma scanning for abnormalities and making dynamic contact with neuronal somata and synapses [28]. After tissue damage, microglia also extend their processes and migrate to the injury site [43] where they change retract their processes changing their shape and phagocytose cells and other debris. It is not completely understood whether glycolytic pathways or oxidative phosphorylation power microglial motility and phagocytosis, but it can be speculated that these processes represent a significant energy demand in the brain [12].

The bioenergetics of microglia in physiological conditions have been elegantly revised by Ghosh *et al.* [44]; hence, this will only be briefly addressed here. Evidence indicates that microglia rely on both glycolytic and oxidative energy metabolism depending on the activation state [44,45]. A comparative transcriptional profiling of genes related to energy metabolism in neurons, astrocytes, and microglia of mouse brain revealed that microglia express the set of genes required for both glycolytic and oxidative energy metabolism [46]. Non-activated microglia has been suggested to rely mainly on oxidative phosphorylation

for ATP production [47–49], while activated microglia, conversely, has been shown to favor glycolysis. In support of the later, increased lactate production and decreased ATP production associated with mitochondrial function were detected in a microglia cell line upon activation with lipopolysaccharides [50,51].

Glucose seems to be the essential fuel for microglia, although these cells are capable of utilizing additional substrates for energy production. Microglia are able to take up glucose and lactate through various GLUTS (although GLUT3 seems to be predominantly expressed) and MCTs, respectively [45]. Glucose may follow a glycolytic fate and TCA cycle processing thereafter. Microglia are also capable of metabolizing ketone bodies such as acetoacetate and β-hydroxybutyrate, which may act as metabolic signals [52–54]. This emerging role of ketone bodies in microglia metabolism is further discussed in the following sections. Although lipid metabolism is not prominent in the brain, it has been suggested that microglia take up and process fatty acids via lipoprotein lipase. Furthermore, microglia express the long-chain fatty acyl-CoA synthetase, which catalyzes the formation of fatty acyl-CoA that in turn is β-oxidized into acetyl-CoA and can be further metabolized in the TCA cycle [46]. Glutamine is a key energy substrate for brain cells, particularly neurons [55]. This vital amino acid may also serve as an important energy substrate in microglia as it has been shown that the glutamine receptors SLC1A5 and SLC38A1 are expressed in these cells enabling them to take up glutamine [46]. Inside the mitochondria, glutamine is converted to glutamate, which is further metabolized by the enzyme glutamate dehydrogenase to α-ketoglutarate, which can enter the TCA cycle and fuel ATP production.

Mechanisms by which energy metabolism affects microglia-derived inflammation are just starting to be unraveled. However, mitochondrial function, glucose availability, and glycolytic rate have been shown to influence pro-inflammatory gene expression at both transcriptional and posttranslational levels [44]. In line with this, it was shown that activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), a metabolic sensor, reduced LPS-induced inflammation in the microglial cell line BV-2 cells [56]. Furthermore, in primary microglia cultures, 2-deoxy-D-glucose, a blocker of the glycolytic pathway, diminishes TNF-α and IL-6 production by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [57].

Neuronal and non-neuronal cells including microglia utilize the energy yielded in the form of ATP from glucose metabolism for cell survival, generation of key molecules involved in neurotransmission, and maintenance of general brain homeostasis. Perturbations in the tight regulation of energy metabolism may be the pathophysiological substrate of many brain disorders. Investigations to identify additional connections between microglia energy metabolism and microglial function, particularly in neurodegeneration, are starting to emerge.

Altered Brain Energy Metabolism in Neurodegenerative Disorders

Neurodegenerative disorders are a broad spectrum of syndromes affecting the CNS. These are characterized by progressive neuronal dystrophic structural alterations, loss of function, and ultimately cell death. At present, there is no curative treatment for such disorders, and the drugs currently available have imperceptible or limited effect on the clinical course [58]. Among the most prevalent and devastating neurodegenerative disorders are AD and PD, while HD, MS, and ALS are less common. These disorders share several pathological characteristics at a subcellular level including abnormal protein aggregation, failure in protein degradation pathways, impaired axonal transport, and overall bioenergetic and mitochondrial dysfunction [59]. A large body of evidence indicates that brain metabolic alterations strongly influence the genesis and progression of neurodegenerative disorders. Functional neuroimaging studies including positron-emission tomography (PET) analyses using fluoro-deoxyglucose uptake into brain cells have shown reduced regional glucose utilization in the brain of patients suffering from AD, PD, ALS, and HD [16–18,60–62]. Moreover, epidemiological studies indicate that metabolic disturbances and syndromes such as high blood pressure, obesity, diabetes, and atherosclerosis may be risk factors for dementia [63]. Therefore, deficits in energy metabolism particularly glucose hypometabolism and mitochondrial dysfunction are highly regarded as early indicators of neurodegenerative disease pathology.

Notably, the studies summarized below are representative evidence of alterations in brain energy metabolism (neuronal and astrocytic metabolism) in several neurological conditions, and such summary does not attempt to be a comprehensive collection of the vast literature available regarding this field (for an extensive review, the reader is referred to Ref. [14]).

Dementia is an umbrella term for a set of symptoms including prominent cognitive decline that is often associated with aging. AD is the most common cause of late-onset dementia causing as many as 50% to 70% of all dementia cases [64]. AD ethiopathology includes plaques of amyloid β (Aβ) peptides and neurofibrillary tangles of hyperphosphorylated tau protein. These are linked to synapse loss and neuronal death, leading to cognitive decline [65]. Compromised brain energy metabolism is a prominent feature in aging and AD pathology [32]. Interestingly, alterations in expression levels and

activities of transporters and metabolic enzymes have been reported in this neurodegenerative disorder. For instance, in mouse models of AD, decreased GLUT1 levels were found to exacerbate amyloid pathology, neurodegeneration, and cognitive function [66]. Reduced levels of GLUT1 and GLUT3 have been observed in the brain of AD patients [67,68], which correlated with decreased brain glucose uptake and subsequent cognitive decline [69]. In addition, a dramatic loss of activity of glycolytic enzymes such as phosphofructokinase, phosphoglycerate mutase, aldolase, G6P isomerase, and LDH was found in brain tissue of AD patients compared to age-matched controls [70]. Moreover, pyruvate dehydrogenase complex [71], cytochrome oxidase [72], and α-ketoglutarate dehydrogenase complex [73] were also seen to be decreased in AD brains. Interestingly, ketogenic substance and nicotinamide supplementation has been effective to reduce Aβ and Tau pathologies and to improve behavioral responses [74].

PD is characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta and their projections to the caudate–putamen of the basal ganglia, which play an essential role in motor function [75]. Glucose hypometabolism in PD brains has also been documented using neuroimaging methods in patients [76]. Notably, mutations in genes associated with early-onset inherited forms of PD (Parkin, PINK1, LRRK2, α-synuclein) result in mitochondrial dysfunction [77]. Furthermore, α-synuclein in plasma has been shown to regulate glucose uptake [78]. Decreased levels of the PPP enzymes G6P-dehydrogenase and 6-phosphogluconate dehydrogenase have been detected at early stages in the putamen and cerebellum of PD brains [79], while G6P-isomerase has been identified as an altered key participant in dopamine metabolism and degeneration in neurons derived from PD animal models [80]. Interventions directed to improve mitochondrial bioenergetics have been shown to ameliorate neuropathology and motor deficits in animal models of PD [81].

ALS (Lou Gehrig's disease) is the most common adult motor neuron disease. It has been shown that ALS patients display increased systemic energy expenditure at rest and are hypercatabolic [82]. In line with this, a recent metabolomics analysis identified increased glycolysis and deficits in amino acid metabolism in a cellular model of ALS. It has been hypothesized that the overall increase in energy demand may reflect major cellular activity to stimulate CNS and muscle repair in an attempt to control the ALS neurodegenerative process [83]. To warrant high levels of ATP production, mitochondria activity and number may increase resulting in enhanced production and release of ROS, which potentially could reach neurotoxic levels [84]. In addition, metabolic alterations including glucose intolerance [85] and insulin resistance [86] have been reported in ALS patients and animal models as well as alterations in blood–brain barrier properties and molecules [87] resulting in increased permeability of the blood–brain barrier and therefore abnormal composition of the cerebrospinal fluid. Together, these findings indicate that altered metabolic homeostasis is associated with ALS pathology.

Although MS is perceived to result from an autoimmune effect of T cells targeting the myelin sheath, MS is a complex CNS disorder in which impaired energy metabolism, particularly mitochondrial dysfunction, has a substantial role [60,88]. Early studies suggesting the involvement of defective pyruvate metabolism in MS were performed by Jones *et al.* [89] in the 1950s. Elevated blood pyruvate levels were found in both fasting and postprandial periods in MS patients with relapse [89]. Later, increased pyruvate levels and α-ketoglutarate were also observed in this disease [90]. In addition, the association between disturbed pyruvate metabolism and MS progression was further strengthened by increased levels of TCA cycle metabolites such as α-ketoglutarate and citrate found in MS patients [91,92]. Increased activity of metabolic enzymes including enolase, pyruvate kinase, LDH, and aldolase in the brain of MS patients has also been detected [93]. Several mitochondrial abnormalities have been identified in MS. For instance, it has been observed that both the number and activity of mitochondria in MS plaques are increased [94]. Moreover, mitochondrial proteins are overexpressed in MS lesions where diminished ATP synthase expression has been detected [95]. Specifically, complex IV activity was significantly increased [96].

HD is a genetic neurodegenerative disorder linked to trinucleotide (CAG) repeat expansions in the huntingtin gene. HD is associated with degeneration and loss of neurons in the striatum causing incessant involuntary movements and motor impairments [97]. Using system-wide analysis of the spatial proteome combined with mass spectrometric analysis, we have recently identified alterations in key proteins related to brain energy metabolism, particularly, glia metabolism in a mouse model of HD [15]. Striatal metabolism has been shown to be decreased prior to atrophy, and interestingly, disease progression is strongly correlated with glucose hypometabolism [98]. In line with this, it has been observed that at early stages of striatum degeneration HD patients display decreased brain glucose uptake [99]. Expression of GLUT3 has been shown to be diminished in the striatum and cortex of HD mice compared to wild-type mice [100]. Interestingly, increasing copy numbers of the gene encoding GLUT3 correlated with a delayed disease onset in HD patients, and overexpression of GLUT3,

phosphofructokinase, and G6P-dehydrogenase protects against development of HD phenotypes in animal models [101]. Finally, evidence suggests that up-regulation of sirtuins, which have been proposed to act as metabolic sensors, may protect striatal neurons against degeneration possibly by preserving mitochondrial function [102,103]. These studies indicate that interventions that improve neuronal bioenergetics may ameliorate HD pathogenesis.

Conclusive evidence strongly supports that altered brain metabolic homeostasis plays a major role in the initiation and progression of neurodegenerative disorders. However, the wealth of knowledge regarding brain energy metabolism function and dysfunction in disease context has been mainly focus on the neuronal and astrocytic compartment, while the intricacies of microglial energy metabolism in neurodegeneration have just begun to be discovered.

Microglial Metabolism and Neurodegenerative Disorders

Microglia and metabolism in AD

”It is well recognized that neurodegenerative diseases are accompanied by deficits in brain energy metabolism [13–15,32]. Neuroinflammation, particularly derived from microglia activation, is also believed to contribute to such brain disorders. However, the bioenergetic mechanisms involved in the neurotoxic or neuroprotective functions of microglia are still unresolved and the studies available in this area are limited.

AD pathophysiology has been associated with increased oxidative stress and neuroinflammation, process in which microglia has been significantly implicated [6]. During disease progression, microglia may assume a useful role, and then progress into a dysfunctional phenotype, which ultimately becomes detrimental. In support of a direct link between aberrant microglial functions and AD, recent transcriptomic studies of microglia in normal and Aβ- mice identified microglial subpopulations defined as disease-associated microglia (DAM). DAMs are located around Aβ plaques and display dysregulated expression of housekeeping, and host-defense genes [104]. At present, little is known about the link between microglia bioenergetics, neuroinflammation, and brain energy failure in AD neurodegeneration. Recently, sophisticated neuroimaging studies using multiple-tracer PET revealed the apparent coexistence of neuroinflammation and elevated glucose consumption in animal models of AD pathology and brain ischemia [105,106]. This may seem paradoxical as it has been consistently demonstrated that glucose hypometabolism is a disease marker of the AD brain. Backes *et al.* [105] claimed that inflammatory cells in diseased brains managed to consume comparable amounts of glucose per time and tissue volume as neurons and astrocytes consume during healthy conditions. Given that brain immune cells are capable of harvesting high amounts of glucose and non-oxidatively metabolize the substrate in reduced oxygen and glucose conditions, those observations suggest that energy metabolism of brain inflammatory cells (including microglia) may be masking metabolic deficits in regions with neuronal damage.

Previous studies have shown that Aβ-plaques in the AD brain elicit inflammatory responses, which may also be reflected systemically in plasma. Treatment with AD plasma was found to affect cellular bioenergetics in a microglial cell line by up-regulating glycolytic flux and enzyme expression arguably to compensate for mitochondrial dysfunction and decreased cell viability [107]. This observation supports the increasing body of evidence that inflammation and energy metabolism are closely linked phenomena in which microglial energetics may also have a significant contribution.

Modulating microglia activity by controlling microglial energy metabolism may represent an innovative approach to hinder neurodegenerative processes. In support of this, targeting the microglial potassium (K_{ATP}) channels has been shown to be effective in controlling inflammatory microglia activation, avoiding its toxic phenotype though a mitochondria-dependent mechanism [108]. Recently, the triggering receptor expressed on myeloid cells-2 (TREM-2) expressed in microglia has received attention in the field of neurodegeneration as coding variants that increase the risk of AD and other neurodegenerative diseases have been identified [109,110]. A recent study combining metabolomics, RNA sequencing, and system analysis showed that microglia of TREM2-deficient mice with AD-like pathology and of AD patients carrying TREM2 risk variants display anomalous autophagy linked to defective mammalian target of rapamycin (mTOR) signaling, which affects ATP levels and biosynthetic pathways. These findings indicate that TREM2 enables microglial responses by sustaining cellular energetic and biosynthetic metabolism in AD [111].

Microglia and metabolism in PD

Pioneer studies by McGeer *et al.* [112] showed the involvement of activated microglia in PD. In the brain from PD patients, high levels of reactive microglia were found in the substantia nigra and putamen [112], and it has been shown that activated microglia may exacerbate neurodegeneration in PD brains [113]. In addition, the exposure of human neuromelanin discharged from damaged dopamine neurons increases the release of pro-inflammatory molecules

in microglial cultures [31]. Recently, PET studies revealed that PD patients display cortical microglial activation and decreased brain glucose metabolism in early stages of the disease [17] as well as increased microglial activation in the basal ganglia involved in PD pathology [17,114,115]. These findings imply that microglial activation may be a contributing factor in disease progression. However, studies addressing the potential involvement of microglial energy metabolism in PD are scarce.

The mechanism of microglia-mediated neurotoxicity in PD is believed to be linked to the generation of oxidative insults from microglia. In the last decade, novel regulatory roles for microglia in PD pathology have been discovered. For instance, metabolomics profiling in cultured microglia demonstrated that α-synuclein-activated microglia produce cytoskeletal, inflammatory, redox-active, and regulatory proteins. Importantly in the metabolic context, α-synuclein stimulation induced metabolic responses in microglia that modulate the glutamate–glutamine cycle. Specifically, a decrease in intracellular glutamate and an increase in the extracellular concentrations of the amino acid were observed [116]. The glutamate–glutamine cycle is crucial for bioenergetic homeostasis and neurotransmission [117]. In addition, multiple lines of evidence suggest that neurotoxic levels of glutamate in the extracellular space also play a complex role in neurodegenerative diseases [118]. It has been shown that activated microglia may secrete large amounts of glutamate. In line with this, studies using microglia isolated from primary mixed glial cell cultures from mice brain showed that neurotoxicity induced by activated microglia is primarily mediated by released glutamate followed by activation of the glutamate receptor subtype, *N*-methyl-D-aspartate (NMDA) receptor and signaling [119]. Following microglia glutamate secretion and NMDA receptor activation, neuronal mitochondrial respiration was observed to be impaired leading to neuronal energy loss and ultimately cell death [119]. Of note, however, is the fact that *in vivo* evidence that microglial release of glutamate is specifically causing neuronal death is lacking.

A recent study using an animal model of PD reported that ethyl pyruvate (EP), a derivative of pyruvate, inhibits microglial activation *in vivo* in the substantia nigra, suggesting that EP may have therapeutic importance in PD regarding microglia-derived oxidative damage [120].

As mentioned before, activated microglia produce several pro-inflammatory enzymes and cytokines that could potentially lead to neuronal damage. It has been suggested that inhibition of microglial over-activation may be a potential therapeutic strategy to prevent the progression of PD. β-Hydroxybutyrate has been shown to suppress lipopolysaccharide (LPS)-induced inflammation in a microglial cell line BV-2 and to protect dopaminergic neurons [121]. Furthermore, β-hydroxybutyric acid concentration-dependently attenuated the LPS-induced decrease in dopamine uptake and loss of tyrosine hydroxylase-immunoreactive neurons in a primary mesencephalic neuron/glia mixed culture. β-Hydroxybutyric acid treatment significantly improved the motor dysfunction in a rat PD model induced by intranigral injection of LPS. The beneficial effect of β-hydroxybutyric was attributed to the inhibition of microglial over-activation and protection of dopaminergic neurons in the substantia nigra. This effect was shown to be mediated by G-protein-coupled receptor 109A (GPR109A) and involved the NF-κB signaling pathway, thus inhibiting pro-inflammatory enzyme (iNOS and COX-2) and cytokine (TNF-α, IL-1β, and IL-6) production [52].

Novel potential approaches to regulate microglial immunomodulation in PD include metabolic targets such as AMPK, a critical enzyme in cellular energy homeostasis and glycogen synthase kinase-3β, an enzyme that mediates microglial migration and inflammation-induced neurotoxicity [122,123].

Microglia energy metabolism in HD and other rare disorders

Despite the critical role of microglia in brain pathologies, limited knowledge is available regarding if and how microglial energy metabolism plays a role in neurodegenerative diseases such HD, ALS, and MS, and the cellular mechanisms that govern microglia bioenergetics are just beginning to be defined in those diseases. Since neuroinflammation is an important feature of these disorders and it has been suggested that energy metabolism affects the pro-inflammatory response in microglia, it can be speculated that the bioenergetics of microglia are somehow involved in these brain disease and the therapeutic potential of targeting microglia metabolism requires comprehensive investigation. For instance, in a model of HD, it was found that the mechanisms involved in pyruvate-mediated neuroprotection of striatal neurons include inhibition of microglial activation [124]. It is now recognized that ALS pathophysiology includes chronic microglial activation particularly in the surroundings of deteriorating motor neurons [125]. Energy deficits and oxidative stress are critically implicated in the pathogenesis of MS. However, there is still a need for investigating microglia bioenergetics in this disorder.

Finally, age is the main risk factor for many neurodegenerative diseases. Therefore, aging is a critical process for examination in order to understand the progression and potential intervention in major brain disorders. Specific changes in the metabolic profile of microglia have been documented in aging. For instance, a study using mass spectrometry-based proteomics to compare primary

microglia from young and aged animals revealed alterations in proteins involved in inflammatory signaling, mitochondrial function, and cellular metabolism, particularly proteins responsible for the breakdown of amino acids and the conversion of ketone bodies into succinyl-CoA. The findings are claimed to indicate that microglia from aged mice display changes in energy regulation that might underlie the alterations in inflammatory signaling [126]. However, the possibility that changes in energy regulation are a result of the exacerbated inflammatory environment cannot be discarded. Neuroinflammation and oxidative stress have been associated with non-pathological aging in humans and animal models. Functional decline of mitochondria in microglia has been shown to produce an exacerbated generation of ROS and inflammatory mediators. Accumulation of mitochondrial DNA oxidative damage in microglia during aging promotes ROS production, which in turn may also increase oxidative stress. Many of these changes are also observed in neurodegenerative conditions, and thus, it is unclear whether these alterations are reactive to the underlying pathophysiology.

Conclusions and Future Directions

Microglial pleiotropic functions range from CNS development and homeostasis to active surveillance of the brain and prompt immune response to injury and infection. Microglia (dys)functions, particularly neuroinflammatory actions, have been identify as a key participant in neurodegenerative disorders. These disorders are accompanied by well-documented deficits in brain energy metabolism, although the current knowledge is based mainly on neurons and astrocytes. Furthermore, analysis of the molecular mechanisms relevant for microglia reprogramming toward regenerative functions points to the crucial role of energy metabolism in shaping microglial functions. Manipulation of metabolic pathways might provide new therapeutic strategies to prevent the detrimental effects of abnormal inflammatory microglia and to control exacerbated inflammation in brain disorders (see Fig. 2). Therefore, current and future research regarding microglia-specific metabolic changes in neurodegeneration should be directed to further understand energy metabolic pathways in microglia, molecular mechanism involved in phenotype selection and to unravel how energy metabolism influences inflammatory process. One approach that may prove to be valuable is the use and development of improved *in vitro* microglia models that more closely recapitulate healthy and disease states. Such models are emerging and include microglia derived from human-induced pluripotent stem cells (hiPSCs), which hold great promise particularly to study specific disease phenotypes. However, hiPSCs have the main caveat that they do not reflect the effects of aging. In addition, one of the main challenges is to accurately generate the different microglial activation phenotypes and the complex interplay between several cell types in brain which are difficult to model in cell culture. Finally, as our understanding of microglia physiology increases, they key involvement of microglial bioenergetics in neurodegeneration is being unravel and novel therapeutic avenues in neurodegenerative disorders will be open.

Acknowledgments

The author apologizes to those colleagues whose work was not recognized due to space constraints or unintentional omission. The author thanks Thomas William Woofenden for proofreading the manuscript.

Received 11 December 2018;
Received in revised form 22 February 2019;
Accepted 5 March 2019
Available online 13 March 2019

Keywords:
glucose metabolism;
microglial activation;
mitochondria;
neurodegenerative disorders;
neuroinflammation

Special issue: Dementia, Brain Disorders and Molecular Mechanisms

Abbreviations used:
AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPK, adenosine monophosphate-activated protein kinase; ETC, electron transport chain; G6P, glucose-6-phosphate; GLUT, glucose transporter; HD, Huntington disease; LDH, lactate dehydrogenase; MCTs, monocarboxylate transporters; MS, multiple sclerosis; PD, Parkinson's disease; PET, positron-emission tomography; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TCA, tricarboxylic acid; TREM, triggering receptor expressed on myeloid cells.

References

[1] H. Kettenmann, U.K. Hanisch, M. Noda, A. Verkhratsky, Physiology of microglia, Physiol. Rev. 91 (2011) 461–553.
[2] V. Hughes, Microglia: the constant gardeners, Nature. 485 (2012) 570–572.

[3] D. Davalos, J.K. Ryu, M. Merlini, K.M. Baeten, N. Le Moan, M.A. Petersen, et al., Fibrinogen-induced perivascular microglial clustering is required for the development of axonal damage in neuroinflammation, Nat. Commun. 3 (2012) 1227.
[4] S. Ghosh, R.L. Geahlen, Stress granules modulate SYK to cause microglial cell dysfunction in Alzheimer's disease, EBioMedicine. 2 (2015) 1785–1798.
[5] M.J. Vasek, C. Garber, D. Dorsey, D.M. Durrant, B. Bollman, A. Soung, et al., A complement–microglial axis drives synapse loss during virus-induced memory impairment, Nature. 534 (2016) 538–543.
[6] C. Cunningham, Microglia and neurodegeneration: the role of systemic inflammation, Glia. 61 (2013) 71–90.
[7] N.C. Derecki, N. Katzmarski, J. Kipnis, M. Meyer-Luehmann, Microglia as a critical player in both developmental and late-life CNS pathologies, Acta Neuropathol. 128 (2014) 333–345.
[8] N. Cartier, C.A. Lewis, R. Zhang, F.M. Rossi, The role of microglia in human disease: therapeutic tool or target? Acta Neuropathol. 128 (2014) 363–380.
[9] C. Cunningham, D.C. Wilcockson, S. Campion, K. Lunnon, V.H. Perry, Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration, J. Neurosci. 25 (2005) 9275–9284.
[10] S.C. Vlad, D.R. Miller, N.W. Kowall, D.T. Felson, Protective effects of NSAIDs on the development of Alzheimer disease, Neurology. 70 (2008) 1672–1677.
[11] D. Attwell, S.B. Laughlin, An energy budget for signaling in the grey matter of the brain, J. Cereb. Blood Flow Metab. 21 (2001) 1133–1145.
[12] E. Engl, D. Attwell, Non-signalling energy use in the brain, J. Physiol. 593 (2015) 3417–3429.
[13] J.V. Andersen, S.K. Christensen, B.I. Aldana, J.D. Nissen, H. Tanila, H.S. Waagepetersen, Alterations in cerebral cortical glucose and glutamine metabolism precedes amyloid plaques in the APPswe/PSEN1dE9 mouse model of Alzheimer's disease, Neurochem. Res. 42 (2017) 1589–1598.
[14] S. Camandola, M.P. Mattson, Brain metabolism in health, aging, and neurodegeneration, EMBO J. 36 (2017) 1474–1492.
[15] N.H. Skotte, J.V. Andersen, A. Santos, B.I. Aldana, C.W. Willert, A. Norremolle, et al., Integrative characterization of the R6/2 mouse model of Huntington's disease reveals dysfunctional astrocyte metabolism, Cell Rep. 23 (2018) 2211–2224.
[16] R.A. Sperling, P.S. Aisen, L.A. Beckett, D.A. Bennett, S. Craft, A.M. Fagan, et al., Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7 (2011) 280–292.
[17] P. Edison, I. Ahmed, Z. Fan, R. Hinz, G. Gelosa, K. Ray Chaudhuri, et al., Microglia, amyloid, and glucose metabolism in Parkinson's disease with and without dementia, Neuropsychopharmacology. 38 (2013) 938–949.
[18] J. Diehl-Schmid, T. Grimmer, A. Drzezga, S. Bornschein, M. Riemenschneider, H. Forstl, et al., Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study, Neurobiol. Aging 28 (2007) 42–50.
[19] R.M. Ransohoff, How neuroinflammation contributes to neurodegeneration, Science. 353 (2016) 777–783.
[20] D. Nayak, T.L. Roth, D.B. McGavern, Microglia development and function, Annu. Rev. Immunol. 32 (2014) 367–402.
[21] M.W. Salter, S. Beggs, Sublime microglia: expanding roles for the guardians of the CNS, Cell. 158 (2014) 15–24.
[22] P.M. Bilimoria, B. Stevens, Microglia function during brain development: new insights from animal models, Brain Res. 1617 (2015) 7–17.
[23] H. Nakanishi, Microglial functions and proteases, Mol. Neurobiol. 27 (2003) 163–176.
[24] R.M. Ransohoff, B. Engelhardt, The anatomical and cellular basis of immune surveillance in the central nervous system, Nat. Rev. Immunol. 12 (2012) 623–635.
[25] D.P. Schafer, E.K. Lehrman, A.G. Kautzman, R. Koyama, A.R. Mardinly, R. Yamasaki, et al., Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner, Neuron. 74 (2012) 691–705.
[26] H. Wake, A.J. Moorhouse, S. Jinno, S. Kohsaka, J. Nabekura, Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals, J. Neurosci. 29 (2009) 3974–3980.
[27] C.L. Hsieh, M. Koike, S.C. Spusta, E.C. Niemi, M. Yenari, M.C. Nakamura, et al., A role for TREM2 ligands in the phagocytosis of apoptotic neuronal cells by microglia, J. Neurochem. 109 (2009) 1144–1156.
[28] A. Nimmerjahn, F. Kirchhoff, F. Helmchen, Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo, Science. 308 (2005) 1314–1318.
[29] C.N. Parkhurst, W.B. Gan, Microglia dynamics and function in the CNS, Curr. Opin. Neurobiol. 20 (2010) 595–600.
[30] R.B. Banati, J. Gehrmann, P. Schubert, G.W. Kreutzberg, Cytotoxicity of microglia, Glia. 7 (1993) 111–118.
[31] H. Wilms, L. Zecca, P. Rosenstiel, J. Sievers, G. Deuschl, R. Lucius, Inflammation in Parkinson's diseases and other neurodegenerative diseases: cause and therapeutic implications, Curr. Pharm. Des. 13 (2007) 1925–1928.
[32] F. Yin, H. Sancheti, I. Patil, E. Cadenas, Energy metabolism and inflammation in brain aging and Alzheimer's disease, Free Radic. Biol. Med. 100 (2016) 108–122.
[33] M. Kobayashi, H. Konishi, T. Takai, H. Kiyama, A DAP12-dependent signal promotes pro-inflammatory polarization in microglia following nerve injury and exacerbates degeneration of injured neurons, Glia. 63 (2015) 1073–1082.
[34] S. Lehnardt, Innate immunity and neuroinflammation in the CNS: the role of microglia in Toll-like receptor-mediated neuronal injury, Glia. 58 (2010) 253–263.
[35] H. Alle, A. Roth, J.R. Geiger, Energy-efficient action potentials in hippocampal mossy fibers, Science. 325 (2009) 1405–1408.
[36] M. Belanger, I. Allaman, P.J. Magistretti, Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation, Cell Metab. 14 (2011) 724–738.
[37] P.J. Magistretti, I. Allaman, A cellular perspective on brain energy metabolism and functional imaging, Neuron. 86 (2015) 883–901.
[38] G. van Hall, M. Stromstad, P. Rasmussen, O. Jans, M. Zaar, C. Gam, et al., Blood lactate is an important energy source for the human brain, J. Cereb. Blood Flow Metab. 29 (2009) 1121–1129.
[39] A. Nehlig, Brain uptake and metabolism of ketone bodies in animal models, Prostaglandins Leukot. Essent. Fat. Acids 70 (2004) 265–275.
[40] H.R. Zielke, C.L. Zielke, P.J. Baab, Direct measurement of oxidative metabolism in the living brain by microdialysis: a review, J. Neurochem. 109 (Suppl. 1) (2009) 24–29.

[41] D.G. Nicholls, L. Johnson-Cadwell, S. Vesce, M. Jekabsons, N. Yadava, Bioenergetics of mitochondria in cultured neurons and their role in glutamate excitotoxicity, J. Neurosci. Res. 85 (2007) 3206–3212.
[42] M.A. Yenari, R.G. Giffard, Ischemic vulnerability of primary murine microglial cultures, Neurosci. Lett. 298 (2001) 5–8.
[43] D. Davalos, J. Grutzendler, G. Yang, J.V. Kim, Y. Zuo, S. Jung, et al., ATP mediates rapid microglial response to local brain injury in vivo, Nat. Neurosci. 8 (2005) 752–758.
[44] S. Ghosh, E. Castillo, E.S. Frias, R.A. Swanson, Bioenergetic regulation of microglia, Glia. 66 (2018) 1200–1212.
[45] M.J. Kalsbeek, L. Mulder, C.X. Yi, Microglia energy metabolism in metabolic disorder, Mol. Cell. Endocrinol. 438 (2016) 27–35.
[46] Y. Zhang, K. Chen, S.A. Sloan, M.L. Bennett, A.R. Scholze, S. O'Keeffe, et al., An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex, J. Neurosci. 34 (2014) 11929–11947.
[47] E. Bernhart, M. Kollroser, G. Rechberger, H. Reicher, A. Heinemann, P. Schratl, et al., Lysophosphatidic acid receptor activation affects the C13NJ microglia cell line proteome leading to alterations in glycolysis, motility, and cytoskeletal architecture, Proteomics. 10 (2010) 141–158.
[48] B. Chenais, H. Morjani, J.C. Drapier, Impact of endogenous nitric oxide on microglial cell energy metabolism and labile iron pool, J. Neurochem. 81 (2002) 615–623.
[49] D.W. Moss, T.E. Bates, Activation of murine microglial cell lines by lipopolysaccharide and interferon-gamma causes NO-mediated decreases in mitochondrial and cellular function, Eur. J. Neurosci. 13 (2001) 529–538.
[50] J. Gimeno-Bayon, A. Lopez-Lopez, M.J. Rodriguez, N. Mahy, Glucose pathways adaptation supports acquisition of activated microglia phenotype, J. Neurosci. Res. 92 (2014) 723–731.
[51] L.A. Volobouéva, J.F. Emery, X. Sun, R.G. Giffard, Inflammatory response of microglial BV-2 cells includes a glycolytic shift and is modulated by mitochondrial glucose-regulated protein 75/mortalin, FEBS Lett. 587 (2013) 756–762.
[52] S.P. Fu, J.F. Wang, W.J. Xue, H.M. Liu, B.R. Liu, Y.L. Zeng, et al., Anti-inflammatory effects of BHBA in both in vivo and in vitro Parkinson's disease models are mediated by GPR109A-dependent mechanisms, J. Neuroinflammation 12 (2015) 9.
[53] C. Huang, P. Wang, X. Xu, Y. Zhang, Y. Gong, W. Hu, et al., The ketone body metabolite beta-hydroxybutyrate induces an antidepression-associated ramification of microglia via HDACs inhibition-triggered Akt-small RhoGTPase activation, Glia. 66 (2018) 256–278.
[54] J.C. Newman, E. Verdin, Ketone bodies as signaling metabolites, Trends Endocrinol. Metab. 25 (2014) 42–52.
[55] H.S. Waagepetersen, H. Qu, U. Sonnewald, K. Shimamoto, A. Schousboe, Role of glutamine and neuronal glutamate uptake in glutamate homeostasis and synthesis during vesicular release in cultured glutamatergic neurons, Neurochem. Int. 47 (2005) 92–102.
[56] C.C. Chen, J.T. Lin, Y.F. Cheng, C.Y. Kuo, C.F. Huang, S.H. Kao, et al., Amelioration of LPS-induced inflammation response in microglia by AMPK activation, Biomed. Res. Int. 2014 (2014), 692061.
[57] Q. Wang, Y. Zhao, M. Sun, S. Liu, B. Li, L. Zhang, et al., 2-Deoxy-D-glucose attenuates sevoflurane-induced neuroinflammation through nuclear factor-kappa B pathway in vitro, Toxicol. in Vitro 28 (2014) 1183–1189.
[58] T.M. Barchet, M.M. Amiji, Challenges and opportunities in CNS delivery of therapeutics for neurodegenerative diseases, Expert Opin. Drug. Deliv. 6 (2009) 211–225.
[59] M.P. Mattson, W.A. Pedersen, W. Duan, C. Culmsee, S. Camandola, Cellular and molecular mechanisms underlying perturbed energy metabolism and neuronal degeneration in Alzheimer's and Parkinson's diseases, Ann. N. Y. Acad. Sci. 893 (1999) 154–175.
[60] Adiele RC, Adiele CA. Metabolic defects in multiple sclerosis. Mitochondrion. 2017.
[61] S. Hoyer, Normal and abnormal circulation and oxidative metabolism in the aging human brain, J. Cereb. Blood Flow Metab. 2 (Suppl. 1) (1982) S10–S13.
[62] S. Hoyer, Abnormalities in brain glucose utilization and its impact on cellular and molecular mechanisms in sporadic dementia of Alzheimer type, Ann. N. Y. Acad. Sci. 695 (1993) 77–80.
[63] M. Kivipelto, T. Ngandu, T. Laatikainen, B. Winblad, H. Soininen, J. Tuomilehto, Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study, Lancet Neurol. 5 (2006) 735–741.
[64] B. Imtiaz, A.M. Tolppanen, M. Kivipelto, H. Soininen, Future directions in Alzheimer's disease from risk factors to prevention, Biochem. Pharmacol. 88 (2014) 661–670.
[65] D.M. Holtzman, J.C. Morris, A.M. Goate, Alzheimer's disease: the challenge of the second century, Sci. Transl. Med. 3 (2011) 77sr1.
[66] E.A. Winkler, Y. Nishida, A.P. Sagare, S.V. Rege, R.D. Bell, D. Perlmutter, et al., GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration, Nat. Neurosci. 18 (2015) 521–530.
[67] S.D. Harr, N.A. Simonian, B.T. Hyman, Functional alterations in Alzheimer's disease: decreased glucose transporter 3 immunoreactivity in the perforant pathway terminal zone, J. Neuropathol. Exp. Neurol. 54 (1995) 38–41.
[68] I.A. Simpson, K.R. Chundu, T. Davies-Hill, W.G. Honer, P. Davies, Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with Alzheimer's disease, Ann. Neurol. 35 (1994) 546–551.
[69] S.M. Landau, D. Harvey, C.M. Madison, E.M. Reiman, N.L. Foster, P.S. Aisen, et al., Comparing predictors of conversion and decline in mild cognitive impairment, Neurology. 75 (2010) 230–238.
[70] P. Iwangoff, R. Armbruster, A. Enz, W. Meier-Ruge, Glycolytic enzymes from human autoptic brain cortex: normal aged and demented cases, Mech. Ageing Dev. 14 (1980) 203–209.
[71] E.K. Perry, R.H. Perry, B.E. Tomlinson, G. Blessed, P.H. Gibson, Coenzyme A-acetylating enzymes in Alzheimer's disease: possible cholinergic 'compartment' of pyruvate dehydrogenase, Neurosci. Lett. 18 (1980) 105–110.
[72] S.J. Kish, C. Bergeron, A. Rajput, S. Dozic, F. Mastrogiacomo, L.J. Chang, et al., Brain cytochrome oxidase in Alzheimer's disease, J. Neurochem. 59 (1992) 776–779.
[73] G.E. Gibson, K.F. Sheu, J.P. Blass, A. Baker, K.C. Carlson, B. Harding, et al., Reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease, Arch. Neurol. 45 (1988) 836–840.
[74] Y. Kashiwaya, C. Bergman, J.H. Lee, R. Wan, M.T. King, M.R. Mughal, et al., A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease, Neurobiol. Aging 34 (2013) 1530–1539.
[75] J.M. Savitt, V.L. Dawson, T.M. Dawson, Diagnosis and treatment of Parkinson disease: molecules to medicine, J. Clin. Invest. 116 (2006) 1744–1754.

[76] P. Borghammer, M. Chakravarty, K.Y. Jonsdottir, N. Sato, H. Matsuda, K. Ito, et al., Cortical hypometabolism and hypoperfusion in Parkinson's disease is extensive: probably even at early disease stages, Brain Struct. Funct. 214 (2010) 303–317.
[77] A.M. Pickrell, R.J. Youle, The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease, Neuron. 85 (2015) 257–273.
[78] G. Rodriguez-Araujo, H. Nakagami, H. Hayashi, M. Mori, T. Shiuchi, Y. Minokoshi, et al., Alpha-synuclein elicits glucose uptake and utilization in adipocytes through the Gab1/PI3K/Akt transduction pathway, Cell. Mol. Life Sci. 70 (2013) 1123–1133.
[79] L. Dunn, G.F. Allen, A. Mamais, H. Ling, A. Li, K.E. Duberley, et al., Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease, Neurobiol. Aging 35 (2014) 1111–1115.
[80] A.L. Knight, X. Yan, S. Hamamichi, R.R. Ajjuri, J.R. Mazzulli, M.W. Zhang, et al., The glycolytic enzyme, GPI, is a functionally conserved modifier of dopaminergic neurodegeneration in Parkinson's models, Cell Metab. 20 (2014) 145–157.
[81] K. Tieu, C. Perier, C. Caspersen, P. Teismann, D.C. Wu, S.D. Yan, et al., D-Beta-hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease, J. Clin. Invest. 112 (2003) 892–901.
[82] B. Funalot, J.C. Desport, F. Sturtz, W. Camu, P. Couratier, High metabolic level in patients with familial amyotrophic lateral sclerosis, Amyotroph. Lateral Scler. 10 (2009) 113–117.
[83] M.J. Rodriguez, N. Mahy, Neuron-microglia interactions in motor neuron degeneration. The inflammatory hypothesis in amyotrophic lateral sclerosis revisited, Curr. Med. Chem. 23 (2016) 4753–4772.
[84] M. Liesa, O.S. Shirihai, Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure, Cell Metab. 17 (2013) 491–506.
[85] P.F. Pradat, G. Bruneteau, P.H. Gordon, L. Dupuis, D. Bonnefont-Rousselot, D. Simon, et al., Impaired glucose tolerance in patients with amyotrophic lateral sclerosis, Amyotroph. Lateral Scler. 11 (2010) 166–171.
[86] E.T. Reyes, O.H. Perurena, B.W. Festoff, R. Jorgensen, W.V. Moore, Insulin resistance in amyotrophic lateral sclerosis, J. Neurol. Sci. 63 (1984) 317–324.
[87] I. Niebroj-Dobosz, P. Janik, B. Sokolowska, H. Kwiecinski, Matrix metalloproteinases and their tissue inhibitors in serum and cerebrospinal fluid of patients with amyotrophic lateral sclerosis, Eur. J. Neurol. 17 (2010) 226–231.
[88] D. Mathur, G. Lopez-Rodas, B. Casanova, M.B. Marti, Perturbed glucose metabolism: insights into multiple sclerosis pathogenesis, Front. Neurol. 5 (2014) 250.
[89] H.H. Jones, H.H. Jones Jr., L.D. Bunch, Biochemical studies in multiple sclerosis, Ann. Intern. Med. 33 (1950) 831–840.
[90] P. Ervenich, New viewpoints in treatment and etiology of multiple sclerosis. II, Arztl Forsch 7 (I) (1953) 55–64.
[91] D.H. Henneman, M.D. Altschule, R.M. Goncz, Carbohydrate metabolism in brain disease. II. Glucose metabolism in schizophrenic, manic-depressive, and involutional psychoses, AMA Arch. Intern. Med. 94 (1954) 402–416.
[92] B. McArdle, I.C. Mackenzie, G.R. Webster, Studies on intermediate carbohydrate metabolism in multiple sclerosis, J. Neurol. Neurosurg. Psychiatry 23 (1960) 127–132.
[93] J.A. Royds, W.R. Timperley, C.B. Taylor, Levels of enolase and other enzymes in the cerebrospinal fluid as indices of pathological change, J. Neurol. Neurosurg. Psychiatry 44 (1981) 1129–1135.
[94] M.E. Witte, L. Bo, R.J. Rodenburg, J.A. Belien, R. Musters, T. Hazes, et al., Enhanced number and activity of mitochondria in multiple sclerosis lesions, J. Pathol. 219 (2009) 193–204.
[95] K.J. Smith, H. Lassmann, The role of nitric oxide in multiple sclerosis, Lancet Neurol. 1 (2002) 232–241.
[96] W.T. Regenold, P. Phatak, M.J. Makley, R.D. Stone, M.A. Kling, Cerebrospinal fluid evidence of increased extramitochondrial glucose metabolism implicates mitochondrial dysfunction in multiple sclerosis disease progression, J. Neurol. Sci. 275 (2008) 106–112.
[97] C.A. Ross, S.J. Tabrizi, Huntington's disease: from molecular pathogenesis to clinical treatment, Lancet Neurol. 10 (2011) 83–98.
[98] A. Antonini, K.L. Leenders, R. Spiegel, D. Meier, P. Vontobel, M. Weigell-Weber, et al., Striatal glucose metabolism and dopamine D2 receptor binding in asymptomatic gene carriers and patients with Huntington's disease, Brain. 119 (Pt 6) (1996) 2085–2095.
[99] A. Ciarmiello, M. Cannella, S. Lastoria, M. Simonelli, L. Frati, D.C. Rubinsztein, et al., Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease, J. Nucl. Med. 47 (2006) 215–222.
[100] H. McClory, D. Williams, E. Sapp, L.W. Gatune, P. Wang, M. DiFiglia, et al., Glucose transporter 3 is a rab11-dependent trafficking cargo and its transport to the cell surface is reduced in neurons of CAG140 Huntington's disease mice, Acta Neuropathol. Commun. 2 (2014) 179.
[101] A. Vittori, C. Breda, M. Repici, M. Orth, R.A. Roos, T.F. Outeiro, et al., Copy-number variation of the neuronal glucose transporter gene SLC2A3 and age of onset in Huntington's disease, Hum. Mol. Genet. 23 (2014) 3129–3137.
[102] H. Jeong, D.E. Cohen, L. Cui, A. Supinski, J.N. Savas, J.R. Mazzulli, et al., Sirt1 mediates neuroprotection from mutant huntingtin by activation of the TORC1 and CREB transcriptional pathway, Nat. Med. 18 (2011) 159–165.
[103] J. Fu, J. Jin, R.H. Cichewicz, S.A. Hageman, T.K. Ellis, L. Xiang, et al., Trans-(–)-epsilon-Viniferin increases mitochondrial sirtuin 3 (SIRT3), activates AMP-activated protein kinase (AMPK), and protects cells in models of Huntington disease, J. Biol. Chem. 287 (2012) 24460–24472.
[104] Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, et al. A unique microglia type associated with restricting development of Alzheimer's disease. Cell. 2017;169:1276-90 e17.
[105] H. Backes, M. Walberer, A. Ladwig, M.A. Rueger, B. Neumaier, H. Endepols, et al., Glucose consumption of inflammatory cells masks metabolic deficits in the brain, Neuroimage. 128 (2016) 54–62.
[106] M. Brendel, F. Probst, A. Jaworska, F. Overhoff, V. Korzhova, N.L. Albert, et al., Glial activation and glucose metabolism in a transgenic amyloid mouse model: a triple-tracer PET study, J. Nucl. Med. 57 (2016) 954–960.
[107] T. Jayasena, A. Poljak, N. Braidy, G. Smythe, M. Raftery, M. Hill, et al., Upregulation of glycolytic enzymes, mitochondrial dysfunction and increased cytotoxicity in glial cells treated with Alzheimer's disease plasma, PLoS One 10 (2015), e0116092.
[108] M.J. Rodriguez, M. Martinez-Moreno, F.J. Ortega, N. Mahy, Targeting microglial K(ATP) channels to treat neurodegenerative diseases: a mitochondrial issue, Oxidative Med. Cell. Longev. 2013 (2013), 194546.
[109] D.L. Kober, T.J. Brett, TREM2–ligand interactions in health and disease, J. Mol. Biol. 429 (2017) 1607–1629.

[110] J.D. Ulrich, T.K. Ulland, M. Colonna, D.M. Holtzman, Elucidating the role of TREM2 in Alzheimer's disease, Neuron. 94 (2017) 237–248.
[111] Ulland TK, Song WM, Huang SC, Ulrich JD, Sergushichev A, Beatty WL, et al. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. Cell. 2017;170:649-63 e13.
[112] P.L. McGeer, S. Itagaki, B.E. Boyes, E.G. McGeer, Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains, Neurology. 38 (1988) 1285–1291.
[113] P.L. McGeer, E.G. McGeer, Inflammation and neurodegeneration in Parkinson's disease, Parkinsonism Relat. Disord. 10 (Suppl. 1) (2004) S3–S7.
[114] A. Gerhard, N. Pavese, G. Hotton, F. Turkheimer, M. Es, A. Hammers, et al., In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease, Neurobiol. Dis. 21 (2006) 404–412.
[115] S. Iannaccone, C. Cerami, M. Alessio, V. Garibotto, A. Panzacchi, S. Olivieri, et al., In vivo microglia activation in very early dementia with Lewy bodies, comparison with Parkinson's disease, Parkinsonism Relat. Disord. 19 (2013) 47–52.
[116] A.D. Reynolds, I. Kadiu, S.K. Garg, J.G. Glanzer, T. Nordgren, P. Ciborowski, et al., Nitrated alpha-synuclein and microglial neuroregulatory activities, J. NeuroImmune Pharmacol. 3 (2008) 59–74.
[117] L.K. Bak, A. Schousboe, H.S. Waagepetersen, The glutamate/GABA-glutamine cycle: aspects of transport, neurotransmitter homeostasis and ammonia transfer, J. Neurochem. 98 (2006) 641–653.
[118] J. Lewerenz, P. Maher, Chronic glutamate toxicity in neurodegenerative diseases—what is the evidence? Front. Neurosci. 9 (2015) 469.
[119] H. Takeuchi, S. Jin, J. Wang, G. Zhang, J. Kawanokuchi, R. Kuno, et al., Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner, J. Biol. Chem. 281 (2006) 21362–21368.
[120] S.H. Huh, Y.C. Chung, Y. Piao, M.Y. Jin, H.J. Son, N.S. Yoon, et al., Ethyl pyruvate rescues nigrostriatal dopaminergic neurons by regulating glial activation in a mouse model of Parkinson's disease, J. Immunol. 187 (2011) 960–969.
[121] S.P. Fu, S.N. Li, J.F. Wang, Y. Li, S.S. Xie, W.J. Xue, et al., BHBA suppresses LPS-induced inflammation in BV-2 cells by inhibiting NF-kappaB activation, Mediat. Inflamm. 2014 (2014) 983401.
[122] E. Pena-Altamira, F. Prati, F. Massenzio, M. Virgili, A. Contestabile, M.L. Bolognesi, et al., Changing paradigm to target microglia in neurodegenerative diseases: from anti-inflammatory strategy to active immunomodulation, Expert Opin. Ther. Targets 20 (2016) 627–640.
[123] S.R. Subramaniam, H.J. Federoff, Targeting microglial activation states as a therapeutic avenue in Parkinson's disease, Front. Aging Neurosci. 9 (2017) 176.
[124] J.K. Ryu, S.U. Kim, J.G. McLarnon, Blockade of quinolinic acid-induced neurotoxicity by pyruvate is associated with inhibition of glial activation in a model of Huntington's disease, Exp. Neurol. 187 (2004) 150–159.
[125] J.S. Henkel, D.R. Beers, W. Zhao, S.H. Appel, Microglia in ALS: the good, the bad, and the resting, J. NeuroImmune Pharmacol. 4 (2009) 389–398.
[126] A. Flowers, H. Bell-Temin, A. Jalloh, S.M. Stevens Jr., P.C. Bickford, Proteomic anaysis of aged microglia: shifts in transcription, bioenergetics, and nutrient response, J. Neuroinflammation 14 (2017) 96.