Journal of Research in Medical and Dental Science
2018, Volume 6, Issue 5, Page No: 223-237

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Do Neurons Require Astrocyte-Derived Lactate for Energy? Astrocyte-Neuron Metabolic Coupling is Mediated by Calcium Waves and Sodium Current in the Tripartite Synapse: Therapeutic Implications for Some Brain Diseases Involving Metabolic Dysregulation

Menizibeya O Welcome*

Department of Physiology, College of Health Sciences, The Nile University of Nigeria, Nigeria

ABSTRACT

The most widely accepted model of brain glucose metabolism is the astrocyte-neuron lactate shuttle (ANLS) hypothesis. However, in recent times, ANLS has met serious criticism as the model could not account for new data indicating that neurons may not require astrocyte-derived lactate for energy. Proponents of the hypothesis still believe that ANLS describes key aspects of brain glucose metabolism and holds therapeutic promise for some brain diseases including mental and substance disorders. Indeed dysfunctions of metabolic machinery of both astrocytes and neurons have been implicated in diseases involving cerebral glucose metabolic dysregulation, suggesting that these cells play a synergic role in glucose metabolism. Unfortunately, however, the cellular and molecular nexus linking astrocyte-to-neuron metabolism has not been fully unraveled. In this review, data on opposing views of brain glucose metabolism are reconciled. It is suggested that metabolic machinery of astrocytes and neurons is coupled to each other via calcium waves and sodium current, mediated by the tripartite synapse, an anatomo-physiologic spatiotemporal integration site, formed by the physical proximity of the membranes of presynaptic neuron, postsynaptic neuron, and astrocyte. The therapeutic implication of this view of astrocyte-neuron glucose metabolism is also discussed.

Key words: Cerebral metabolism, ANLS, Tripartite synapse, Calcium waves, Sodium current

HOW TO CITE THIS ARTICLE: Menizibeya O Welcome*, Do neurons require astrocyte-derived lactate for energy? Astrocyte-neuron metabolic coupling is mediated by Calcium waves and Sodium current in the tripartite synapse: Therapeutic implications for some brain diseases involving metabolic dysregulation, J Res Med Dent Sci, 2018, 6 (5):223-237

Corresponding author: Menizibeya O Welcome
e-mail✉: welcome.menizibeya@nileuniversity.edu.ng
Received: 03/09/2018
Accepted: 28/09/2018

INTRODUCTION

Glucose is the main energy substrate required for brain functioning [1,2]. Of the ~160 g of glucose required by the body per day, about 120 g–130 g per day is used by the brain at resting physiological state. Upon brain activation, this quantity increases up to about 140 g–150 g per day. The cerebral glucose level is maintained within a narrow range, and it is about 10%–30% of the blood glucose concentration. However, glucose level in different regions of the brain differ substantially, and may range from 1.4 mM to 2.5 mM, depending on a couple of factors including physiological state (e.g. fasting, fed state), energy reserve, duration of mental activity, some diseases, drug use and misuse [1,2]. Furthermore, brain regions poor in blood brain barrier such as the median eminence may have a substantially higher glucose level compared to other regions of the brain [3–6].

Other substrates such as ketone bodies, fatty acids, and some amino acids can serve as energy substrates for brain activities especially during prolonged fasting. However, in the absence of glucose, other energy substrates cannot maintain normal functioning of the brain [1,2,7,8]. Thus, prolonged fasting results to hypoglycemia, which may, in turn lead to neurological symptoms that may subsequently progress to loss of consciousness, coma, and eventually, death, if adequate measures are not taken to avert the decreasing blood glucose [9,10]. Significant decrease in brain functions following reduction in blood glucose level [8], accompanied by a corresponding decrease in cerebral glucose level has been reported by different laboratories around the world [11–15]. However, excessive increase in blood glucose level is associated with disease states such as diabetes mellitus

and prediabetes. Chronic hyperglycemia observed in diabetes mellitus can predispose the individual to neurological and cardiovascular complications such as neuropathy, nephropathy, and stroke [10]. Accumulating data indicate that prediabetic glycemic level is also a potential risk factor for neurological and especially cardiovascular diseases [16–18]. Thus both hypoglycemic and hyperglycemic states pose serious health consequences for the individual. However, under normal physiological state, both chronic hypoglycemia and hyperglycemia are prevented through a series of physiologic response, involving timely sensing of decreasing or increasing glucose level with secretion of corresponding hormones [19–21]. Insulin is the major hormone that counteracts increasing blood sugar above the threshold, whereas counter-regulatory hormones such as glucagon, adrenaline, cortisol, and growth hormone serve to return decreasing blood glucose level to normal [22,23]. It is believed that the counter-regulatory responses to decreasing glycemic level are mainly controlled by the brain and involve coordinated activities of neurons and astrocytes, as well as peripheral organs such as pancreas, liver, muscle, carotid bodies, adrenal glands, small intestines, and adipose tissue [24–26]. Indeed neurons have been shown to control response of peripheral organs to changes in blood glucose level [27,28]. Consequently, malfunctions of cerebral mechanisms that control glycemic levels within normal range can potentially lead to disorders in regulation of blood and cerebral glucose levels [20,21]. Apart from diabetes mellitus and prediabetes, disorders in brain glucose metabolism have been reported in obesity, multiple sclerosis, Alzheimer's, Parkinson, Huntington diseases [29–33], and more recently, in schizophrenia [34]. It should be mentioned that these diseases constitute a significant portion of the global burden of diseases with immense economic consequences on sufferers, families, caregivers, and public health [35–39]. Though new evidences [40,41] indicate that the disorders in brain glucose metabolism may involve defects in specific receptors, in particular, GLUT2 and sweet taste receptors that control glucose transport and sensing in the brainstem and hypothalamus, the mechanisms are yet to be completely understood. It is, however, possible that brain glucose sensing is cooperatively linked to cellular uptake of this energy substrate. Thus understanding the precise mechanisms of brain glucose metabolism is essential in addressing the gaps in the literature that may lead to new frontiers in treatment of diseases, involving dysfunctions in brain glucose metabolism.

Cerebral glucose metabolism has been traditionally explained with hypothesis and models. The most widely accepted model of brain glucose metabolism is the astrocyte-neuron lactate shuttle (ANLS) hypothesis [42]. The hypothesis posits that cerebral glucose metabolism is initiated by glutamate activation of astrocyte membrane transporters or receptors, released from the presynaptic terminal of neuron (Figure 1). Glutamate transport into astrocytes stimulates synthesis of astrocyte-derived lactate *via* glycolysis (Figure 1). This lactate diffuses out *via* the astrocyte monocarboxylate transporter types 1 and 4 (*MCT-1* and *MCT-4*), and translocates into neurons *via MCT2*. In neurons, lactate undergoes further metabolic reactions in the tricarboxylic acid (TCA) cycle to produce more ATP and other substances required for neuronal functioning [43,44].

In Figure 1, Glucose is transported into astrocytes *via* GLUT1 glucose transporter of the blood brain barrier. In astrocytes, glucose is either stored as glycogen or under the influence of neutrally released glutamate (Glu), channeled to glycolytic pathway, where for each molecule of glucose two NADH and four ATP and two lactate molecules are produced for NADH or two ATP molecules consumed in the process [45–48]. (The Glu is transported to astrocyte where it is converted to Gln and channeled back to neuron. Details on glutamate-glutamine cycling are presented in Figure 2). The glycogen depot is believed to be a temporary store that power astrocyte energy needs, especially during cortical stimulation [49, 50]. Lactate is released into the extracellular space *via* proton coupled transporter of lactate, ketone bodies and pyruvate–monocarboxylate transporters (MCTs, MCT1 and MCT4). The astrocyte-derived lactate diffuses into neurons *via* MCT2. However, lactate can be transported from the blood into neurons or astrocytes *via* MCT1, which is expressed in the cerebral endothelium [45,51]. In both neurons and astrocytes, depending on the rate of energy dissipation, lactate can be converted to pyruvate and back by lactate dehydrogenase type 1 (LDH-1, also known as LDHB or LDH-H) and type 5 (LDH-5, also known as LDHA or LDHM) respectively [52-55]. Pyruvate is channeled for mitochondrial TCA and oxidative phosphorylation in both neurons and astrocytes through the activities of pyruvate dehydrogenase [55].

Recent evidences have revealed several shortcomings of the ANLS hypothesis [19,56]. Despite modifications of this hypothesis [30,50,57], proponents still believe that the hypothesis addresses key aspects of cerebral glucose metabolism [58]. However, recent reports [59-64] indicate that the ANLS hypothesis requires revision due to its inability to account for recent findings, suggesting that neuronal function remains unaltered in the absence of astrocyte-derived lactate. Surprisingly, however, lactate appears to be an integral metabolite and substrate for memory and cognitive functions [47,65-67], and thus, holds promise for treatment of some brain diseases including mental and substance disorders [68-72]. Though the chief source has remained elusive for several decades, cerebral lactate is produced by both astrocytes and neurons under physiological conditions [73]. In aerobic conditions where cerebral lactate is readily converted to pyruvate for mitochondrial TCA cycle and oxidative phosphorylation, the level of cerebral lactate is maintained at physiological range (0.5–1 mmol/l) [74]. Despite its relatively small mass (2% of

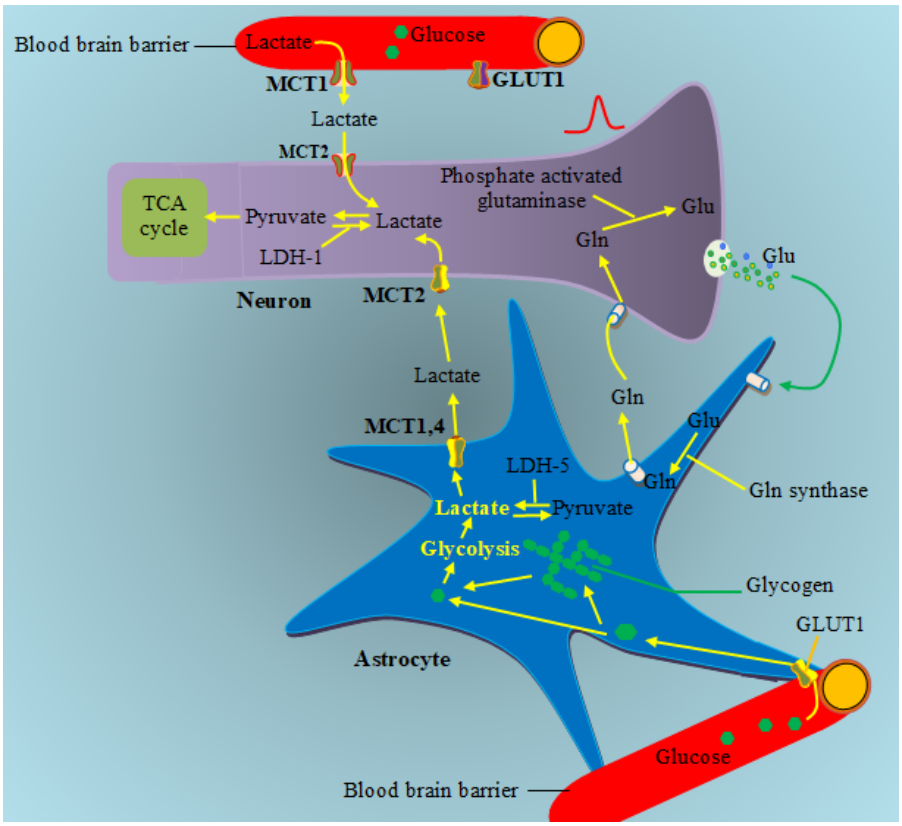

Figure 1: A schematic representation showing the major dogma of the astrocyte-neuron lactate shuttle (ANLS) hypothesis

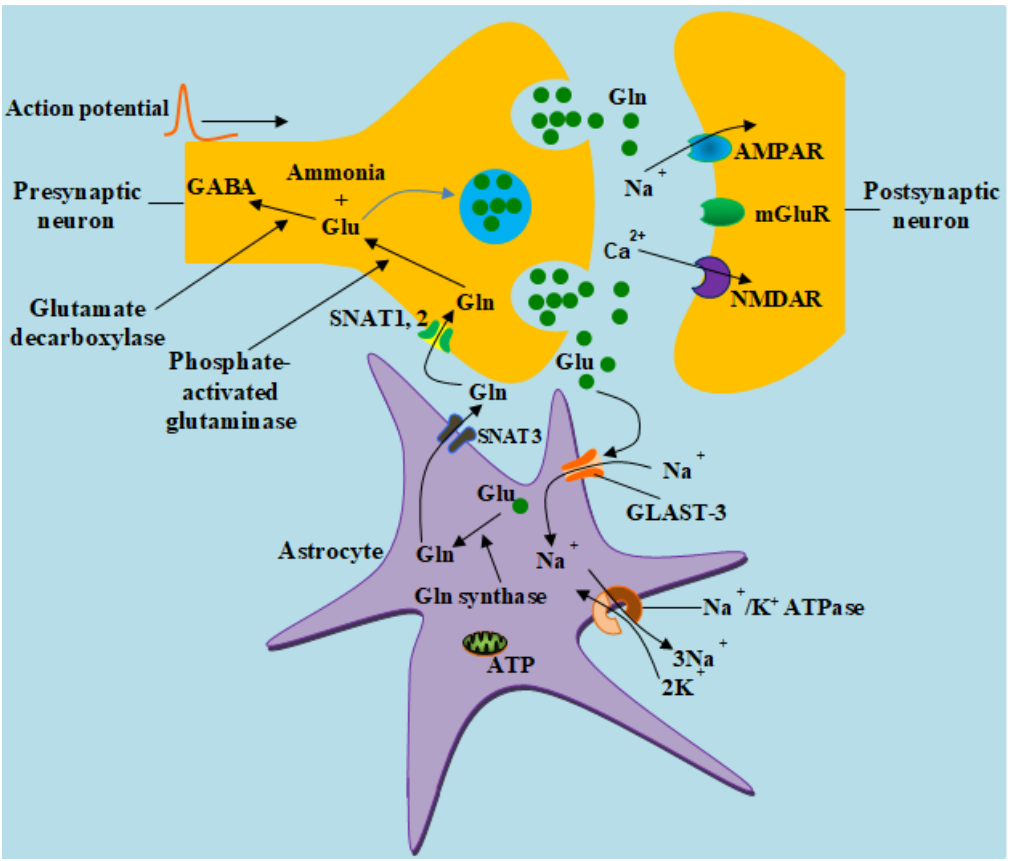

Figure 2: Glutamate-glutamine cycling is coupled to sodium homeostasis and metabolism

typical human body mass), human brain, accounting for 20%–25% of the total body glucose consumption rate (~5.6 mg glucose per 100 g human brain tissue per minute) [73,75], requires 20% of body oxygen utilization (i.e. 3.5 ml of O_2 per 100 g of brain tissue or ~49 ml O_2 per minute at physiological state [76]. So, in anaerobic conditions, there is increased production of lactate, which will be ultimately converted to pyruvate for further metabolic reactions that will lead to production of more ATP and other molecules required for astrocyte and neuronal functions [77]. Though excessive increase in lactate resulting from neuropathologies (e.g. cerebral injury, hypoxia, cerebral ischemia, neurodegenerative diseases, cerebral aging, and shock) has been shown to be detrimental to brain tissue, the cellular roles of different levels of increase in cerebral lactate on neuronal functions have not been fully unraveled [74,77-80]. For instance, in cerebral ischemia, oxygen supply to brain tissue substantially reduces within a few seconds, ATP stores become depleted within a few minutes, so that the brain resorts to anaerobic metabolism for its primary source of energy molecules [81]. In such neuropathophysiological conditions, which are often characterized by failure of oxidative mechanisms and impaired lactate clearance, cerebral lactate concentration can exceed 4–5 mmol/l [74,82]. It should be mentioned that though high lactate concentration is seen both in neuropathologies and high intensity exercise, cerebral lactate in the latter [74,79,80] is readily removed through MCT1 [74]. In contrast, neuropathological elevation of cerebral lactate is associated with impaired glucose or monocarboxylate transporters [74]. For instance, LDH-5 dysfunction has been implicated in certain cancers, in which lactate is produced at a high rate (Warburg effect) [83,84]. The Warburg effect is believed to play a role in pathogenesis of neurodegenerative diseases such as Alzheimer's disease [85]. So, in Alzheimer's disease brain, metabolism is reduced especially in hippocampus by about 20%–25% compared to healthy adults [86]. Indeed several researchers have shown 8%–50% decrease in glucose metabolic rate in mild cognitive impairment and neurodegenerative diseases [86]. Based on these data, some researchers have successfully shown in animal models that LDH inhibition (e.g. by stiripentol) suppressed seizures in epilepsy [53]. The recent developments about lactate as a signaling molecule that may function as a neuro-transmitter or -hormone indicate that lactate may be a key molecule for memory formation and neuroprotection [67]. Lactate readily binds to GPR81 (hydroxycarboxylic receptor 1, HCA1), but the pathways are yet to be delineated [87]. Administration of supraphysiologic concentration of L-lactate has been found to alleviate symptoms of some brain diseases [72,87].

Indeed disorders in both astrocyte and neuron metabolism have been reported in several diseases involving cerebral glucose metabolic dysregulation including obesity, diabetes mellitus, multiple sclerosis, Alzheimer's, and Parkinson diseases, suggesting that these cells play a synergic role in glucose metabolism [88-93]. Unfortunately, however, the cellular and molecular nexus linking astrocyte-neuron metabolism is not completely understood.

In this review, data on opposing views of brain glucose metabolism are reconciled. It is suggested that while neuron may not depend on astrocyte-derived lactate for energy, neuron-derived lactate is coupled to astrocyte lactate production *via* calcium waves and sodium current, mediated by the tripartite synapse, an anatomo-physiologic spatiotemporal integration site, formed by the physical proximity of the membranes of presynaptic neuron, postsynaptic neuron, and astrocyte. The therapeutic implication of this view of astrocyte-neuron glucose metabolism is also discussed.

Emergence of models of cerebral glucose metabolism

The fact that glucose is an integral metabolic substrate for brain functioning has been known for almost a century. However, the mechanisms of glucose uptake, transport and metabolism by brain cells have remained an unending debate. The mechanisms of regulation of brain glucose metabolism remained a speculation until the early 1990s when different laboratories around the world began reporting the chief role of lactate derived from astrocyte glycolysis in the production of energy for neuronal functions [42,94-98]. This led to the formulation of the first hypothesis about brain glucose metabolism (ANLS), put forward by Pellerin and Magistretti (vide supra) [42]. Around the same time, Ferrer et al. [99], Leloup et al. [100], Jetton et al. [101], and Ozcan et al. [102] reported the discovery of some glucose sensors in neurons and astrocytes. The identification of *GLUT2* [100], K-ATP [103,101] and *SGLT3* [104,105] as members of the glucose sensors located on the plasma membrane of neurons and astrocytes in hypothalamus, brainstem [59-64], amygdala and nucleus accumbens [5] was integral in defining the glucosensor model of cerebral glucose metabolism. The recent identification of sweet taste receptors as astrocyte and neuronal glucose sensors in hypothalamus and brainstem, controlling cerebral glucose metabolism has solidified the glucosensor model of cerebral glucose metabolism [59-64,106]. However, for reasons not clearly understood, the glucosensor model did not attract much attention as did the ANLS hypothesis [42,58,107]. It is possible that the astrocentric view of the ANLS model and neuron-astrocyte cooperativity in metabolic/transmitter cycling could have been responsible. Other possible reasons are discussed below.

Cerebral lactate shuttle: Dissecting the "window" of bidirectional metabolic flow

It was previously thought, on the basis of the ANLS hypothesis, that astrocytes were mainly responsible for trophic functions in the brain, feeding neurons with metabolites [108,109]. However, evidences have shown

that this is unlikely (vide supra). Thus neurons have their metabolic machinery for active production of lactate as well as its metabolic reactions that culminate in production of more ATP and other substances to power neuronal activities. In either scenario, glucose is actively transported from the bloodstream *via* the blood brain barrier to the brain cells, where they undergo glycolysis and oxidative phosphorylation to generate 13% and 87% ATP respectively [1,2,98,110]. Thus, both neurons and astrocytes can potentially generate lactate, which can enter the TCA cycle for further metabolic reactions.

A possible reason for the dominating view of the ANLS hypothesis over the glucosensor model of cerebral glucose metabolism may be due to the peculiar localization of astrocytes to the blood brain barrier, hence, it was thought that these cells are mainly responsible for feeding neurons with metabolic substrates (lactate). Truly, this view was strongly supported by morphological data and expression of isozymes of glucose metabolism. Morphologically, 80% of the astrocyte surface area accounts for processes such as lamellipodia and filopodia, which were thought, may not accommodate considerable quantity of mitochondria [49]. However, a recent report showed that mitochondria in astrocytes are usually located adjacent to the plasma membrane of the lamellipodia and filopodia. Furthermore, similar to neurons, about 16%–22% of the total area of these astrocyte processes is occupied by mitochondria [111]. Again, astrocytes are well suited for aerobic glycolysis due to expression of fructose-2,6-bisphosphatase, lactate dehydrogenase type 5 and pyruvate kinase M2 isoform. Nevertheless, like astrocytes, neurons express glucokinase and can also convert lactate to pyruvate for mitochondrial metabolism due to the expression of lactate dehydrogenase type 1 [46,47,112,113].

In a recent report, it was shown that neurons have higher expression of glucokinase than astrocytes, suggesting that glycolysis in the former may be more active than the latter [46]. This indicates that indeed, there is possibility of flow of lactate from neurons to glial cells, since neurons will have a higher production of lactate [114]. This view completely negates ones of the major tenets of ANLS hypothesis, which posits that astrocyte-derived lactate, is transported to neurons [42,58]. Again, on the basis of previous data, it was believed that only astrocytes express glycogen synthase and glycogen phosphorylase [115], however, recent reports indicate that neurons also express these enzymes [116,117]. Therefore, similar to astrocytes, neurons can carry out a wide range of metabolic activities independent on astrocyte shuttling of lactate. In this paper, it is suggested that there is no rigid compartmentalization of the metabolic machinery of astrocytes and neurons in a living physiological system. Thus, rather than functioning in isolation, astrocyte metabolic activities are coupled to neuronal metabolism *via* calcium waves and sodium currents. These ions represent major ions that control cellular activities [26, 118-121]. Cooperativity between these cells was documented by our group in a previous work [1] and also reported elsewhere [121-126]. Arguably, though, glutamate-glutamine cycling is a crucial example of metabolic cooperativity between astrocytes and neurons (vide infra).

Do neurons really depend on astrocyte-derived lactate for energy? Putting an end to the unending ANLS debate

One of the major contending issues about the ANLS hypothesis is whether or not neuron depends on lactate derived from astrocyte glycolysis for energy [48]. Based on accumulating research evidences, indicating that neurons express glucose-metabolizing enzymes, similar to or even higher in activity compared to those found in astrocytes, opponents of the ANLS hypothesis have argued that neurons can produce considerable amount of lactate required to power their energy needs at rest and especially during brain activation without any need for astrocyte-derived lactate [46, 114]. Lundgaard et al. have showed that glucose is preferentially taken up by neurons in activated mental state [46]. Indeed Lundgaard et al. also reported high expression of hexokinase (the glucose cleaving enzyme of the initial step of glycolysis) in neurons than in astrocytes [46]. Similar findings have been reported by Díaz-García et al. Interestingly, Díaz-García et al. revealed that neuronal metabolism during brain activation does not depend on astrocyte-derived lactate; rather it reflects increased direct glucose consumption by neurons [127]. Furthermore, Díaz-García et al. reported that neuronal metabolism is independent on glutamate-glutamine cycling, suggesting that apart from sodium currents, triggered by neurally released glutamate, other mechanisms may be responsible for astrocyte-neuron glucose metabolic integration or cooperativity [127]. In this paper, it is suggested that calcium homeostasis is integral to the metabolic cooperativity between astrocyte and neuron (vide infra). These results strongly contradict the ANLS, thus the need for further modification or revision.

It should be mentioned that the peculiarities of the ANLS hypothesis in various brain regions may be responsible for the inconsistent data reported by different authors [128,129]. Due to large variance in level of activity, which also, can trigger neuronal metabolism, according to emerging report [130], neurons of the neocortex may actively use up glucose and lactate to power their functional requirements–in such a situation, astrocyte may play a little or no role in shunting of lactate to neurons. In dorsal hippocampus and amygdala, ANLS appears to contribute to memory consolidation and fear conditioning [128]. However, both direct neuronal glucose and astrocyte shuttling of lactate contribute to cerebral metabolism [128]. The recent result reported by Drulis-Fajdasz et al. showed that in hippocampus of young animals, ANLS is very active, whereas aging hippocampal neurons of aged animals are mostly independent on astrocyte derived lactate [129]. In a

recent paper, the originators of the ANLS hypothesis argued that the model does not exclude direct neuronal uptake of glucose [131], which suggests that neurons may not require astrocyte derived lactate since neurons can directly transport glucose for their energy requirements. The recent report by Dienel further showed that neurons may not depend on astrocyte-derived lactate for energy [56]. Dienel also revealed that astrocyte-neuron lactate shuttling does not significantly contribute to brain energetics, especially during mental activation [56]. Similar results were reported by Patel et al. [132], and also documented in other findings [133]. Patel et al. showed that pyruvate derived from neuronal glucose is responsible for feeding neurons with their energy needs during brain activation [132]. However, possibility for lactate shuttling from astrocyte to neuron cannot be completely excluded. Based on a relatively recent model, Mangia et al. suggested that such shuttling can occur provided that neurons remain inactive and astrocyte glucose transport capacity is increased by 12 times [114]. Unfortunately, however, in practice, neither condition has been reported [114]. In fact Dienel et al. even showed that upon physiological activation, breakdown products of glycogen stores in astrocytes are used up by the astrocytes themselves, not neurons [30]. It should be mentioned that in normal physiological condition *in vivo*, cooperativity and integration of information from multiple cells determine continuity of life processes. Indeed dysfunctions of metabolic machinery of both astrocytes and neurons are implicated in diseases involving brain metabolic disorders [58], suggesting that these cells play a synergic role in brain metabolism.

Rather than astrocytes feeding neurons with energy substrates, the nature of metabolic coupling between these brain cells may be synergic and that both glycolysis and oxidative phosphorylation to a considerable extent occur in neurons and astrocytes [134,135]. So, while lactate shuttling may occur between neurons and astrocytes, the basis for such a phenomenon is to maintain energy homeostasis, required for sustained activity of the brain especially during activation [135].

Tripartite synapse: Spatiotemporal integration site for astrocyte-neuron metabolic coupling- The role of calcium waves and sodium currents

The tripartite synapse refers to the anatomo-physiologic spatiotemporal integration site, formed by the physical proximity of the membranes of presynaptic neuron, postsynaptic neuron, and astrocyte [136,137]. The term "tripartite synapse" was introduced in 1994 by Parpura et al. [138] to describe the unique roles of astrocytes in integration of information by direct communication with both pre- and post-synaptic elements *via* neuro- and glio-transmission. Thus these star-shaped structures were more than neuronal support cells that played active roles in brain functioning [137]. The functional implication of this morphological architecture of the astrocyte-neuron junction was not realized until the twenty-first century when a number of authors reported unique roles of this anatomo-physiologic spatiotemporal integration site in modulation of a couple of brain processes in health and disease [139-143]. The tripartite synapse is now believed to play an integral role in synchronizing activities mainly by regulating calcium dynamics [140] and sodium homeostasis [144-146]. These calcium dynamics and sodium homeostasis underlie the cellular switches, controlling metabolic activities in the brain. The coordinated activities of membrane associated calcium and sodium clocks are linked to cytoplasmic oscillatory molecular clocks that regulate uptake, transport and synchronize the homeostasis of these ions with metabolic responses to the metabolic activities of neurons and astrocytes [26].

The tripartite synapse contains multiple sites, which upon activation, induces sodium signals in astrocytes [147]. So, upon activation of glutamatergic neurotransmission, the released glutamate at the presynaptic knob diffuses to the surrounding post-synaptic neuron and astrocyte membrane to activate its cognate receptors/transporters, which evokes inward sodium transients in astrocytes, which may be local or global, depending on the number and duration of activated tripartite synapses (Figure 2) [45,144]. This sodium current is believed to be one of the most important factors that provide the energy required for the movement of a couple of ions, neurotransmitters, fatty acids, amino acids and other molecules across membranes of the cell through the activation of astrocyte uptake and metabolism of glucose [146]. Thus, the anatomical structure formed by these interacting structures known as tripartite synapse, is critical to astrocyte-neuron metabolic integration and cooperativity. Therefore activation of astrocyte sodium ion fluxes mediate neuro-metabolic coupling in the brain [144].

In Figure 2, arrival of action potential triggers the release of glutamate into the synapse. Glutamate (Glu) stimulates its cognate receptor (*mGluR*) at the post-synaptic terminal or translocates into the astrocyte *via* sodium-dependent glutamate transporters with corresponding influx of sodium ions (Excitatory Amino Acid Transporter, EAAT1 or Glutamate Aspartate Transporter, *GLAST-3, EAAT2*, and *EAAT3*) [43]. The Glu in astrocyte is converted to glutamine (Gln) by glutamine synthase. Increase in the level of astrocyte glutamate promotes the release of glutamine *via* SNAT3, a sodium-coupled neutral amino acid transporter that is capable of importing and exporting glutamine. Following its release into the extracellular space, glutamine is taken up by neurons *via* SNAT1 and 2. For each substrate, one sodium ion is cotransported and 1 proton is antiported [148,149]. In neurons glutamine is converted to glutamate and ammonia by phosphate-activated glutaminase. Neuronal glutamate can be metabolized to gamma-aminobutyric acid (GABA) by glutamate decarboxylase or packaged into synaptic vesicles *via* vesicular glutamate transporter (VGLUT)

and released into the synaptic cleft upon glutamatergic activation [48,147]. The influx of sodium ions following glutamate transporter activation in astrocytes generates an inward sodium current, which subsequently activates the Na+/K+ ATPase on the astrocyte plasma membrane [43]. While it is clear that changes in sodium current are integral to initiation of astrocyte metabolism, how neurally released glutamate is coupled to initiation of astrocyte glycolysis has not been completely unraveled. It can be suggested, however, that the mechanism may be related to activity dependent mediation of metabolism *via* increased ion fluxes. Also, sodium currents triggered upon activation of Na+/K+ pump is believed to underlie some of the metabolic processes that are associated with excitatory action of neutrally released glutamate on astrocytes. Indeed glutamate is the major excitatory neurotransmitter in the central nervous system, mainly synthesized in the TCA cycle and recycled between neurons and astrocytes [48,149]. Both astrocytes and neurons can synthesize glutamate from glucose [49]. The expression of pyruvate carboxylase in astrocyte affirms to the ability of these glial cells to mediate synthesis of glutamate from glucose [49].

The sodium-dependent glutamate transporters are the major means of sodium influx into astrocyte (Figure 2). However, sodium can also be transported into astrocyte through connexons, pannexins, Na+ dependent solute carrier transporters, NKCC1 (Na+/K+/2Cl-co-transporter), NBC (Na+/2HCO_3-co-transporter), and other Na+ ion channels [145,150-154]. But connexons and pannexins are channels that can transport sodium in both directions, depending on a number of factors including channel subunit charge [26,155]. A previous report showed that astrocyte-neuron coupling *via* junctional complexes provides metabolic and electrotonic interconnections between the cells. Furthermore, the authors reported that this coupling is genetically determined during the process of ontogenesis [155].

Sodium homeostasis is maintained by the Na+/K+ ATPase, which functions to extrude Na+ in astrocytes by expenditure of energy in the form of ATP produced during sodium influx. This ATPase is believed to utilize about 40% of cellular energy to power this carrier [147]. The activity of this ATPase returns sodium transient to allow for the next cycle of sodium influx [144,156]. Rose et al. suggested that sodium ion functions as a signal molecule in astrocyte-neuron metabolic coupling in health and disease [144]. Indeed glutamate evokes spatiotemporal activity-dependent sodium signaling in astrocytes [145]. The functional consequences of sodium dysregulation in pathophysiological conditions have been previously discussed [145]. Astrocyte sodium ion disorder due to Na+/K+ ATPase dysfunctions has been reported in a couple of diseases involving neurometabolic disorders. In neurodegenerative diseases and senescence (which are also characterized by cerebral glucose dysregulation), decrease in the activity of Na+/K+-ATPase has been reported to cause energy deficiency [157,158]. Na+/K+-ATPase dysfunctions have been documented in other disorders including brain injury, cerebral ischemia, stress, and depression [135]. Na+/K+-ATPase dysfunctions also occur in diabetes mellitus [159,160]. A study by Kinoshita et al. showed the essential role of Na+/K+ ATPase in glio-neuro-protection [161]. Thus positive modulators of sodium pump can be harnessed for health benefits. Interestingly, Sodhi et al. showed that pNaKtide, a peptide that inhibits Na+/K+-ATPase mediated reactive oxygen signaling, improved insulin signaling and metabolism in laboratory animals, indicating that pharmacological agents can be designed to ameliorate the effects of central Na+/K+-ATPase dysfunctions in brain diseases [160,162]. Because Na+/K+-ATPase is also involved in learning and memory, such pharmacological agents may play a role in ameliorating memory deficits in diseases, characterized by both cognitive impairments and glucose metabolic disorders [158]. A couple of preclinical and clinical trials have shown that inhibitors of sodium channels can be successfully used to alleviate the suffering of individuals with certain brain diseases [163-165]. Several pharmacological compounds that act on central sodium channels to relieve the symptoms of cerebral metabolic disorders have been discussed by Waszkielewicz et al. [164]. In multiple sclerosis, Parkinson disease, febrile seizures and neuropsychiatric disorders, voltage-gated sodium channel blockers have been found effective to improve both symptoms and neurometabolic functions of the brain [164,166]. For instance, pharmacological agents such as topiramate and riluzole (voltage-gated sodium channel blockers), exerts neuroprotective effects on the brain, at least in part, by improving sodium ion homeostasis and cerebral metabolic functions as well as neurotransmitter activity [164]. Clinical trial has shown promise for application of sodium channel blockers in multiple sclerosis [167].

The intracellular signaling of sodium *via* the Na+/K+ ATPase in astrocytes is coupled to homeostasis of extracellular and intracellular potassium, calcium and pH in the brain [156]. Indeed neurally-mediated release of glutamate following brain activation has been linked to elevation of cytoplasmic free calcium that propagates as waves from astrocytes to neighboring astrocytes and neurons [168,169]. In response to neurally released glutamate, astrocytes can directly modulate cytoplasmic calcium fluxes and affect transmission of signal by neighboring neurons through changes in calcium levels [170]. In addition to the tripartite synapse participation in ion homeostasis, gap junction connexons and pannexins are essential for the propagation of calcium waves in neurons and astrocytes. The functional implication of this activation lies on several activities of the brain, including metabolism and action potential propagation [119,144,170]. Astrocyte-neuron calcium signaling plays an important role in astrocyte-neuron metabolic coupling *via* regulation of astrocyte and neuronal activity [144,171]. In a recent book, extensive analysis of the

literature revealed that calcium homeostasis in the cell is coupled to mitochondrial metabolism, which in turn is linked to cytosolic calcium waves [26]. Thus calcium waves are critical to astrocyte-neuronal metabolism.

However, apart from glutamate, other neurotransmitters and a couple of gliotransmitters can trigger calcium waves [119]. Increase in neuronal activity will result to increased release of glutamate, which will increase waves of calcium and other ions. This will be associated with increase in energy demand. Thus glycolysis and glycogenolysis, triggered mainly by waves and currents of ion flow, metabolic substrates, hormones and neurotransmitters will increase to maintain the activity level of the cell [43,172]. Calcium inhibitors have been found to have beneficial effects on brain metabolism [165-167]. For instance, blockade of CaV1.3 activity has been found to be effective in Parkinson's disease [165,169]. Indeed patients who are placed on L-type calcium blockers for cardiovascular disease experience substantially reduced risk of Parkinson's disease compared to those who are not on calcium channel blockers or the general population [164]. The GABA derivative, gabapentin, binds to the α2δ subunit of CaV2 channels to inhibit this receptor, thereby relieving neuronal hyperexcitability and symptoms of brain metabolic dysfunctions due to dysregulation of calcium signaling [164]. Several pharmacological compounds that act on central calcium channels have been discussed and are currently in different phases of clinical trials for possible application in brain diseases involving neurometabolic dysfunctions (reviewed in Waszkielewicz et al.) [164]. Though their mechanisms of action vary, dihydropyridines such as nifedipine, nitrendipine, nimodipine and isradipine exhibit neuroprotective effects [164,173,174]. It was previously reported that systemic administration of isradipine in rodents resulted to rejuvenation of dopaminergic neurons and renewed capability to generate autonomous activity [175]. Experimental data have shown that dihydropyridine calcium channel blockers protect against and reduce mortality rate in Parkinson's disease patients [176]. Relatively recent reports have shown that pharmacological inhibition of brain L-type calcium channel isoforms (e.g. Cav1.2 and Cav1.3) may be beneficial in the treatment of brain diseases involving metabolic dysregulation [166]. Although the mechanisms of actions of calcium channel blockers on brain cells have not been completely unraveled, previous studies have suggested that these calcium inhibitors are involved in mediating long-term potentiation and long-term depression [170].

CONCLUSION

This paper reconciled different opposing data on cerebral metabolism and revealed key cellular and molecular nexus linking astrocyte-neuron metabolism. The astrocyte and neuron metabolic machinery is coupled to each other *via* calcium waves and sodium currents, mediated by signaling of glutamate and other transmitters in the tripartite synapse. Glutamate-glutamine cycling ensures cooperativity of astrocyte-neuron metabolism in accordance with the physiological requirements of the brain; however, it does not guarantee neuronal dependency on astrocyte derived lactate. Astrocyte-neurometabolic coupling is essential in normal synaptic functioning, and is critical in health and disease. Inhibitors of specific sodium and calcium channel subtypes expressed in the brain have been found to be beneficial in certain brain diseases involving metabolic dysregulation.

FUTURE DIRECTIONS

Since astrocyte-neurometabolic coupling is associated with ion (e.g. sodium, calcium) homeostasis [1,2,26,144-146], future studies will investigate the effects of pharmacological agents on Na+/K+ ATPase, sodium and calcium ion channels as well as key molecular switches that determine the activity level of these ions and related subsystems in diabetes mellitus, prediabetes, neurodegenerative diseases, and other brain diseases involving metabolic dysregulation. Future investigations on the synergism of astrocyte-neuron metabolism of glucose can provide important data for pharmacological intervention in metabolic brain diseases and cognitive impairments. It is therefore important for future studies to investigate how inhibitors of different sodium and calcium channel subtypes respond to changes in neuronal and astrocyte metabolism in health and disease. This may provide novel information for potential therapeutic application for some brain diseases involving metabolic dysregulation.

CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this paper.

REFERENCES

1. Welcome MO, Mastorakis NE, Pereverzev VA. Sweet taste receptor signaling network: possible implication for cognitive functioning. Neurol Res Int 2015; 2015: 606479.
2. Welcome MO, Pereverzev VA. Glycemic allostasis during mental activities on fasting in non alcohol users and alcohol users with different durations of abstinence. Ann Med Health Sci Res 2014; 4:199-207.
3. Thorens B. Brain glucose sensing and neural regulation of insulin and glucagon secretion. Diabetes Obes Metab 2011; 13:82–8.
4. Burdakov D, Luckman SM, Verkhratsky A. Glucose-sensing neurons of the hypothalamus. Philos Trans R Soc Lond B Biol Sci 2005; 360:2227–35.

5. Koekkoek LL, Mul JD, la Fleur SE. Glucose-sensing in the reward system. Front Neurosci 2017; 11:716.
6. Fioramonti X, Contié S, Song Z, et al. Characterization of glucosensing neuron subpopulations in the arcuate nucleus. Integration in neuropeptide Y and pro-opio melanocortin networks? Diabetes 2007; 56:1219–27.
7. White H, Venkatesh B. Clinical review: Ketones and brain injury. Crit Care 2011; 15:219.
8. Welcome MO, Pereverzeva EV, Pereverzev VA. A novel psychophysiological model of the effect of alcohol use on academic performance of male medical students of Belarusian State Medical University. Int J Collab Res Int Med Public Health 2010; 2:183–97.
9. Hevor TK. Some aspects of carbohydrate metabolism in the brain. Biochimie 1994; 76:111-20.
10. Verberne AJ, Sabetghadam A, Korim WS. Neural pathways that control the glucose counterregulatory response. Front Neurosci 2014; 8:38.
11. McNay EC, Sherwin RS. Effect of recurrent hypoglycemia on spatial cognition and cognitive metabolism in normal and diabetic rats. Diabetes 2004; 53:418–25.
12. McNay EC, Cotero VE. Mini-review: Impact of recurrent hypoglycemia on cognitive and brain function. Physiol Behav 2010; 100:234–8.
13. Hill J, Zhao J, Dash PK. High blood glucose does not adversely affect outcome in moderately brain-injured rodents. J Neurotrauma 2010; 27:1439–48.
14. Tallroth G, Ryding E, Agardh CD. Regional cerebral blood flow in normal man during insulin-induced hypoglycemia and in the recovery period following glucose infusion. Metabolism 1992; 41:717–21.
15. Litvin M, Clark AL, Fisher SJ. Recurrent hypoglycemia: Boosting the brain's metabolic flexibility. J Clin Investig 2013; 123:1922–24.
16. Task Force Members, Rydén L, Grant PJ, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013; 34:3035-87.
17. Singleton JR, Smith AG. Neuropathy associated with prediabetes: What is new in 2007? Cur Diabetes Rep 2007; 7:420–24.
18. Buysschaert M, Medina JL, Bergman M, et al. Prediabetes and associated disorders. Endocrine 2015; 48:371–93.
19. Aronoff SL, Berkowitz K, Shreiner B, et al. Diabetes glucose metabolism and regulation: Beyond insulin and glucagon. Spectrum 2004; 17:183-90.
20. Sprague JE, Arbeláez AM. Glucose counterregulatory responses to hypoglycemia. Pediatr Endocrinol Rev 2011; 9:463-75.
21. Cryer PE. Hierarchy of physiological responses to hypoglycemia: Relevance to clinical hypoglycemia in type I (insulin dependent) diabetes mellitus. Horm Metab Res 1997; 29:92-6.
22. Fan X, Ding Y, Cheng H, et al. Amplified hormonal counter regulatory responses to hypoglycemia in rats after systemic delivery of a SUR-1-selective K(+) channel opener? Diabetes 2008; 57:3327–34.
23. Martín-Timón I, Del Cañizo-Gómez FJ. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. World J Diabetes 2015; 6:912–26.
24. Welcome MO, Dane Ş, Mastorakis NE, et al. Glucoallostasis and higher integrative brain functions, In: Advances in Psychobiology. New York: Nova Science Publishers 2018; 119–36.
25. Welcome MO, Mastorakis NE, Pereverzev VA. Multilevel system coupling of error commission, detection and correction in the error monitoring and processing system are required for high precision task performance, and modulates neural plasticity through changes in glucoallostasis. Int J Med Physiol 2017; 2:27-34.
26. Welcome MO. Gastrointestinal physiology: Development, principles and mechanism of regulation. Cham, Switzerland: Springer Nature 2018.
27. Ruud J, Steculorum SM, Brüninga JC. Neuronal control of peripheral insulin sensitivity and glucose metabolism. Nat Commun 2017; 8:15259.
28. Donovan CM, Watts AG. Peripheral and central glucose sensing in hypoglycemic detection. Physiology (Bethesda) 2014; 29:314–24.
29. Shah K, DeSilva S, Abbruscato T. The role of glucose transporters in brain disease: Diabetes and Alzheimer's disease. Int J Mol Sci 2012; 13:12629–655.
30. Dienel GA, Cruz NF. Nutrition during brain activation: Does cell-to-cell lactate shuttling

contribute significantly to sweet and sour food for thought? Neurochem Int 2004; 45:321–51.

31. Cecchini MP, Fasano A, Boschi F, et al. Taste in Parkinson's disease. J Neurol 2015; 262:806–13.
32. Lee AA, Owyang C. Sugars, sweet taste receptors, and brain responses. Nutrients 2017; 9:653.
33. Cani PD, Holst JJ, Drucker DJ, et al. GLUT2 and the incretin receptors are involved in glucose-induced incretin secretion. Mol Cell Endocrinol 2007; 276:18–23.
34. Jouroukhin Y, Kageyama Y, Misheneva V, et al. DISC1 regulates lactate metabolism in astrocytes: Implications for psychiatric disorders. Transl Psychiatry 2018; 8:76.
35. Bhutani J, Bhutani S. Worldwide burden of diabetes. Indian J Endocrinol Metab 2014; 18:868–70.
36. Mancini MC, de Melo ME. The burden of obesity in the current world and the new treatments available: Focus on liraglutide 3.0 mg. Diabetol Metab Syndr 2017; 9:44.
37. Lopez AD, Murray CC. The global burden of disease, 1990-2020. Nat Med 1998; 4:1241-43.
38. Stovner LJ, Hoff JM, Svalheim S, et al. Neurological disorders in the Global Burden of Disease 2010 study. Acta Neurol Scand Suppl 2014; 198:1-6.
39. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 2017; 16:877-97.
40. Welcome MO, Mastorakis NE. Emerging concepts in brain glucose metabolic functions: From glucose sensing to how the sweet taste of glucose regulates its own metabolism in astrocytes and neurons. NeuroMol Med 2018; 20:281–300.
41. Welcome MO, Mastorakis N, Pereverzev VA, et al. A model system of error commission, detection and correction for high precision error coupling in the error monitoring and processing system: Role of glycemic allostasis regulation. Second International Conference on Mathematics and Computers in Sciences and in Industry, IEEE, Conference Publishing Service, CPS 2015; 145–52.
42. Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: A mechanism coupling neuronal activity to glucose utilization. PNAS 1994; 91:10625–629.
43. Kasischke KA. Activity-Dependent Metabolism in Glia and Neurons. Elsevier 2014.
44. Hubbard JA, Binder DK. Glutamate metabolism. Astrocytes and epilepsy 2016; 197-224.
45. Pierre K, Pellerin L. Monocarboxylate transporters in the central nervous system: Distribution, regulation and function. J Neurochem 2005; 94: 1–14.
46. Lundgaard I, Li B, Xie L, et al. Direct neuronal glucose uptake heralds activity-dependent increases in cerebral metabolism. Nat Commun 2015; 6: 6807.
47. Steinman MQ, Gao V, Alberini CM. The role of lactate-mediated metabolic coupling between astrocytes and neurons in long-term memory formation. Front Integr Neurosci 2016; 10:10.
48. Petroff OA. Metabolic biopsy of the brain. In Molecular Neurology 2007; 77-100.
49. Hertz L, Peng L, Dienel GA. Energy metabolism in astrocytes: High rate of oxidative metabolism and spatiotemporal dependence on glycolysis/glycogenolysis. J Cereb Blood Flow Metab 2007; 27:219–49.
50. DiNuzzo M, Maraviglia B, Giove F. Why does the brain (not) have glycogen? Bioessays 2011; 33:319–26.
51. Rinholm JE, Hamilton NB, Kessarism N, et al. Regulation of oligodendrocyte development and myelination by glucose and lactate. J Neurosci 2011; 31:538–48.
52. Mächler P, Wyss MT, Elsayed M, et al. In vivo evidence for a lactate gradient from astrocytes to neurons. Cell Metab 2016; 23:94-102.
53. Sada N, Lee S, Katsu T, et al. Targeting LDH enzymes with a stiripentol analog to treat epilepsy. Science 2015; 347:1362-7.
54. Bittar PG, Charnay Y, Pellerin L, et al. Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. J Cereb Blood Flow Metab 1996; 16:1079-89.
55. Laughton JD, Bittar P, Charnay Y, et al. Metabolic compartmentalization in the human cortex and hippocampus: Evidence for a cell-and region-specific localization of lactate dehydrogenase 5 and pyruvate dehydrogenase. BMC Neurosci 2007; 8:35.
56. Dienel GA. The metabolic trinity, glucose-glycogen-lactate, links astrocytes and neurons in brain energetics, signaling, memory, and gene expression. Neurosci Lett 2017; 637:18–25.
57. Hertz L, Gibbs ME, Dienel GA. Fluxes of lactate into, from, and among gap junction-coupled astrocytes and their interaction with noradrenaline. Front Neurosci 2014; 8:261.

58. Pellerin L, Bouzier-Sore AK, Aubert A, et al. Activity-dependent regulation of energy metabolism by astrocytes: An update. Glia 2007; 55:1251–62.

59. Benford H, Bolborea M, Pollatzek E, et al. A sweet taste receptor-dependent mechanism of glucosensing in hypothalamic tanycytes. Glia 2017; 65:773–89.

60. Kohno D, Koike M, Ninomiya Y, et al. Sweet taste receptor serves to activate glucose-and leptin-responsive neurons in the hypothalamic arcuate nucleus and participates in glucose responsiveness. Front Neurosci 2016; 10:502.

61. Kohno D. Sweet taste receptor in the hypothalamus: A potential new player in glucose sensing in the hypothalamus. J Physiol Sci 2017; 67:459–65.

62. Ren X, Zhou L, Terwilliger R, et al. Sweet taste signaling functions as a hypothalamic glucose sensor. Front Integr Neurosci 2009; 3:12.

63. Lazutkaite G, Soldà A, Lossow K, et al. Amino acid sensing in hypothalamic tanycytes *via* umami taste receptors. Mol Metab 2017; 6:1480–92.

64. Chao DHM, Argmann C, Van Eijk M, et al. Impact of obesity on taste receptor expression in extra-oral tissues: Emphasis on hypothalamus and brainstem. Sci Rep 2016; 6:29094.

65. Rutkowsky JM, Lee LL, Puchowicz M, et al. Reduced cognitive function, increased blood-brain-barrier transport and inflammatory responses, and altered brain metabolites in LDLr -/-and C57BL/6 mice fed a western diet. PLoS One 2018; 13:e0191909.

66. Suzuki A, Stern SA, Bozdagi O, et al. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 2011; 144:810-23.

67. Proia P, Di Liegro CM, Schiera G, et al. Lactate as a metabolite and a regulator in the central nervous system. Int J Mol Sci 2016; 17:1450.

68. Newman LA, Korol DL, Gold PE. Lactate produced by glycogenolysis in astrocytes regulates memory processing. PLoS One 2011; 6:e28427.

69. Quintard H, Patet C, Zerlauth JB, et al. Improvement of neuroenergetics by hypertonic lactate therapy in patients with traumatic brain injury is dependent on baseline cerebral lactate/ pyruvate ratio. J Neurotrauma 2016; 33:681–7.

70. Bouzat P, Sala N, Suys T, et al. Cerebral metabolic effects of exogenous lactate supplementation on the injured human brain. Intensive Care Med 2014; 40:412-21.

71. Glenn TC, Martin NA, Horning MA, et al. Lactate: Brain fuel in human traumatic brain injury: A comparison with normal healthy control subjects. J Neurotrauma 2015; 32:820-32.

72. Carpenter KL, Jalloh I, Hutchinson PJ. Glycolysis and the significance of lactate in traumatic brain injury. Front Neurosci 2015; 9:112.

73. Goyal MS, Vlassenko AG, Blazey TM, et al. Loss of brain aerobic glycolysis in normal human aging. Cell Metab 2017; 26:353–360.

74. Riske L, Thomas RK, Baker GB, et al. Lactate in the brain: An update on its relevance to brain energy, neurons, glia and panic disorder. Ther Adv Psychopharmacol 2017; 7:85–89.

75. Mergenthaler P, Lindauer U, Dienel GA, et al. Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci 2013; 36:587–597.

76. Jain V, Langham MC, Wehrli FW. MRI estimation of global brain oxygen consumption rate. J Cereb Blood Flow Metab 2010; 30:1598–1607.

77. Larach DB, Kofke WA, Le Roux P. Potential non-hypoxic/ischemic causes of increased cerebral interstitial fluid lactate/pyruvate ratio: A review of available literature. Neurocrit Care 2011; 15:609–622.

78. Jha MK, Morrison BM. Glia-neuron energy metabolism in health and diseases: New insights into the role of nervous system metabolic transporters. Exp Neurol 2018; 309:23–31.

79. Marion DW. Optimum serum glucose levels for patients with severe traumatic brain injury. F1000 Med Rep 2009; 1:42.

80. Ross JM, Öberg J, Brené S, et al. High brain lactate is a hallmark of aging and caused by a shift in the lactate dehydrogenase A/B ratio. PNAS 2010; 107:20087–20092.

81. Robertson CS. Anaerobic metabolism within the brain: its relationship to brain failure in head-injured patients. In: Bihari D, Holaday JW, editors, Brain failure. Update in Intensive Care and Emergency Medicine. Berlin, Heidelberg, Springer; 1989.

82. Phypers B. Lactate physiology in health and disease. Contin Educ Anaesth Crit Care Pain 2006; 6:128–132.

83. Petrelli F, Cabiddu M, Coinu A, et al. Prognostic role of lactate dehydrogenase in solid tumors: A systematic review and meta-analysis of 76 studies. Acta Oncol 2015; 54:961–970.

84. Kennedy KM, Dewhirst MW. Tumor metabolism of lactate: The influence and therapeutic potential for MCT and CD147 regulation. Future Oncol 2010; 6:127.

85. Burns JS, Manda G. Metabolic pathways of

the Warburg effect in health and disease: perspectives of choice, chain or chance. Int J Mol Sci 2017; 18:2755.

86. Cunnane C, Nugent S, Roy M, et al. Brain fuel metabolism, aging and Alzheimer's diseases. Nutrition 2011; 27:3–20.
87. Mosienko V, Teschemacher AG, Kasparov S. Is L-lactate a novel signaling molecule in the brain? J Cereb Blood Flow Metab 2015; 35:1069–1075.
88. Zheng H, Zheng Y, Wang D, et al. Analysis of neuron–astrocyte metabolic cooperation in the brain of db/db mice with cognitive decline using 13C NMR spectroscopy. J Cereb Blood Flow Metab 2017; 37:332–43.
89. Neth BJ, Craft S. Insulin resistance and Alzheimer's disease: Bioenergetic linkages. Front Aging Neurosci 2017; 9:345.
90. Chen Z, Zhong C. Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: Implications for diagnostic and therapeutic strategies. Prog Neurobiol 2013; 108:21-43.
91. Li W, Choudhury GR, Winters A, et al. Hyperglycemia alters astrocyte metabolism and inhibits astrocyte proliferation. Aging Dis 2018; 9:674-84.
92. Kang S, Lee Y, Lee JE. Metabolism-Centric overview of the pathogenesis of Alzheimer's disease. Yonsei Med J 2017; 58:479-88.
93. Douglass JD, Dorfman MD, Thaler JP. Glia: Silent partners in energy homeostasis and obesity pathogenesis. Diabetologia 2017; 60:226–36.
94. Pellerin L, Magistretti PJ. Excitatory amino acids stimulate aerobic glycolysis in astrocytes *via* an activation of the Na+/K+ ATPase. Dev Neurosci 1996; 18:336–42.
95. Yu N, Martin JL, Stella N, et al. Arachidonic acid stimulates glucose uptake in cerebral cortical astrocytes. PNAS 1993; 90:4042–6.
96. Sonnewald U, Westergaard N, Schousboe A. Glutamate transport and metabolism in astrocytes. Glia 1997; 21:56–63.
97. Sokoloff L, Takahashi S, Gotoh J, et al. Contribution of astroglia to functionally activated energy metabolism. Dev Neurosci 1996; 18:344–52.
98. Peng L, Zhang X, Hertz L. High extracellular potassium concentrations stimulate oxidative metabolism in a glutamatergic neuronal culture and glycolysis in cultured astrocytes but have no stimulatory effect in a GABAergic neuronal culture. Brain Res 1994; 663:168–72.
99. Ferrer J, Benito C, Gomis R. Pancreatic islet GLUT2 glucose transporter mRNA and protein expression in humans with and without NIDDM. Diabetes 1995; 44:1369–74.
100. Leloup C, Arluison M, Lepetit N, et al. Glucose transporter 2 (GLUT 2): Expression in specific brain nuclei. Brain Res 1994; 638:221-6.
101. Jetton TL, Liang Y, Pettepher CC, et al. Analysis of upstream glucokinase promoter activity in transgenic mice and identification of glucokinase in rare neuroendocrine cells in the brain and gut. J Biol Chem 1994; 269:3641-54.
102. Ozcan S, Dover J, Rosenwald AG, et al. Two glucose transporters in Saccharomyces cerevisiae are glucose sensors that generate a signal for induction of gene expression. PNAS 1996; 93:12428-32.
103. Ashford MLJ, Boden PR, Treherne JM. Glucose-induced excitation of hypothalamic neurones is mediated by ATP-sensitive K+ channels. Pflugers Arch 1990; 415:479-83.
104. Ashford MLJ, Sturgess NJ, Trout NJ, et al. Adenosine-5′-triphosphate-sensitive ion channels in neonatal rat cultured central neurones. Pflugers Arch 1988; 412:297-304.
105. Dunham I, Shimizu N, Roe BA, et al. The DNA sequence of human chromosome 22. Nature 1999; 402:489-95.
106. Murovets VO, Bachmanov AA, Zolotarev VA. Impaired glucose metabolism in mice lacking the Tas1r3 taste receptor gene. PLoS One 2015; 10: e0130997.
107. Genc S, Kurnaz IA, Ozilgen M. Astrocyte-neuron lactate shuttle may boost more ATP supply to the neuron under hypoxic conditions–in silico study supported by in vitro expression data. BMC Syst Biol 2011; 5:162.
108. Sofroniew MV, Vinters HV. Astrocytes: Biology and pathology. Acta Neuropathol 2010; 119:7-35.
109. Kimelberg HK, Nedergaard M. Functions of astrocytes and their potential as therapeutic targets. Neurotherapeutics 2010; 7: 338-53.
110. Kety SS. The general metabolism of the brain in vivo. In: Richter D (Ed). Metabolism of the nervous system. London: Pergamon 1957; 221-37.
111. Agarwal A, Wu P-H, Hughes EG, et al. Transient opening of the mitochondrial permeability transition pore induces microdomain calcium transients in astrocyte processes. Neuron 2017; 93:587-605.
112. De Backer I, Hussain SS, Bloom SR, et al. CNS Control of Metabolism Insights into the role of neuronal glucokinase. Am J Physiol Endocrinol Metab 2016; 311:E42-55.
113. Levin BE, Routh VH, Kang L, et al. Neuronal

glucosensing: What do we know after 50 years? Diabetes 2004; 53:2521-8.

114. Mangia S, Simpson IA, Vannucci SJ, et al. The in vivo neuron-to-astrocyte lactate shuttle in human brain evidence from modeling of measured lactate levels during visual stimulation. J Neurochem 2009; 109:55-62

115. Wiesinger H, Hamprecht B, Dringen R. Metabolic pathways for glucose in astrocytes. Glia 1997; 21:22-34.

116. Baranowska-Bosiacka I, Falkowska A, Gutowska I, et al. Glycogen metabolism in brain and neurons-astrocytes metabolic cooperation can be altered by pre- and neonatal lead (Pb) exposure. Toxicology 2017; 390:146-58.

117. Pfeiffer-Guglielmi B, Dombert B, Jablonka S, et al. Axonal and dendritic localization of mRNAs for glycogen-metabolizing enzymes in cultured rodent neurons. BMC Neuroscience 2014; 15:70.

118. Parpura V, Verkhratsky A. Homeostatic function of astrocytes: Ca2+ and Na+ signaling. Transl Neurosci 2012; 3: 334-44.

119. Scemes E, Giaume C. Astrocyte calcium waves: What they are and what they do. Glia 2006; 54:716-25.

120. Bernardinelli Y, Magistretti PJ, Chatton J-Y. Astrocytes generate Na+-mediated metabolic waves. Proc Natl Acad Sci 2004; 101:14937-42.

121. Vardjan N, Verkhratsky A, Zorec R. Astrocytic pathological calcium homeostasis and impaired vesicle trafficking in neurodegeneration. Int J Mol Sci 2017; 18:358.

122. Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 2011; 14:724-38.

123. Wade JJ, McDaid LJ, Harkin J, et al. Bidirectional coupling between astrocytes and neurons mediates learning and dynamic coordination in the brain: a multiple modeling approach. PLoS One 2011; 6: e29445.

124. De Keyser J, Mostert JP, Koch MW. Dysfunctional astrocytes as key players in the pathogenesis of central nervous system disorders. J Neurol Sci 2008; 267:3-16.

125. Petit JM, Magistretti PJ. Regulation of neuron-astrocyte metabolic coupling across the sleep-wake cycle. Neuroscience 2016; 323:135-56.

126. Wade J, McDaid L, Harkin J, et al. Self-repair in a bidirectionally coupled astrocyte-neuron (AN) system based on retrograde signaling. Front Comput Neurosci 2012; 6:76.

127. Díaz-García CM, Mongeon R, Lahmann C, et al. Neuronal stimulation triggers neuronal glycolysis and not lactate uptake. Cell Metab 2017; 26:361-74.

128. Kong L, Zhao Y, Zhou W-J, et al. Direct neuronal glucose uptake is required for contextual fear acquisition in the dorsal hippocampus. Front Mol Neurosci 2017; 10:388.

129. Drulis Fajdasz D, Gizak A, Wójtowicz T. Aging associated changes in hippocampal glycogen metabolism in mice. Evidence for and against astrocyte to neuron lactate shuttle. Glia 2018; 66:1481-95.

130. Barros LF, Weber B. CrossTalk proposal: An important astrocyte-to-neuron lactate shuttle couples neuronal activity to glucose utilisation in the brain. J Physiol 2018; 596:347-50.

131. Magistretti PJ, Allaman I. Lactate in the brain: From metabolic end-product to signalling molecule. Nat Rev Neurosci 2018; 19:235-49.

132. Patel AB, Lai JCK, Chowdhury GMI, et al. Direct evidence for activity-dependent glucose phosphorylation in neurons with implications for the astrocyte-to-neuron lactate shuttle. PNAS 2014; 111:5385-90.

133. Hall CN, Klein-Flügge MC, Howarth C, et al. Oxidative phosphorylation, not glycolysis, powers presynaptic and postsynaptic mechanisms underlying brain information processing. J Neurosci 2012; 32:8940-51.

134. Ivanov AI, Malkov AE, Waseem T, et al. Glycolysis and oxidative phosphorylation in neurons and astrocytes during network activity in hippocampal slices. J Cereb Blood Flow Metab 2014; 34:397-07.

135. Kasischke KA, Vishwasrao HD, Fisher PJ, et al. Neural activity triggers neuronal oxidative metabolism followed by astrocytic glycolysis. Science 2004; 305:99-03.

136. Araque A. Tripartite synapses: Glia, the unacknowledged partner. Trends Neurosci 1999; 22:208-15.

137. Gertrudis P. Tripartite synapses: Sstrocytes process and control synaptic information. Trends Neurosci 2009; 32:421-31.

138. Parpura V, Basarsky TA, Liu F, et al. Glutamate-mediated astrocyte-neuron signalling. Nature 1994; 369:744-47.

139. Tewari SG, Majumdar KK. A mathematical model of the tripartite synapse: Astrocyte-induced synaptic plasticity. J Biol Phys 2012; 38:465-96.

140. Farhy-Tselnicker I, Allen NJ. Astrocytes, neurons, synapses: A tripartite view on cortical circuit development. Neural Dev 2018; 13:7.

141. Heller JP, Rusakov DA. The nanoworld of the tripartite synapse: Insights from super-resolution microscopy. Front Cell Neurosci 2017; 11:374.

142. Hillen AEJ, Burbach JPH, Hol EM. Cell adhesion and matricellular support by astrocytes of the tripartite synapse. Prog Neurobiol 2018; 165:66-86.

143. Panatier A, Arizono M, Nägerl UV. Dissecting tripartite synapses with STED microscopy. Philos Trans R Soc Lond B Biol Sci 2014; 369:20130597.

144. Rose CR, Chatton JY. Astrocyte sodium signaling and neuro-metabolic coupling in the brain. Neuroscience 2016; 323:121-34.

145. Rose CR, Karus C. Two sides of the same coin: sodium homeostasis and signaling in astrocytes under physiological and pathophysiological conditions. Glia 2013; 61:1191-05.

146. Rose CR, Verkhratsky A. Principles of sodium homeostasis and sodium signalling in astroglia. Glia 2016; 64:1611-27.

147. Rudy CC, Hunsberger HC, Weitzner DS, et al. The role of the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease. Aging Dis 2015; 6:131-48.

148. Bhutia YD, Ganapathy V. Glutamine transporters in mammalian cells and their functions in physiology and cancer. Biochim Biophys Act Mol Cell Res 2016; 1863:2531-39.

149. Yang CZ, Zhao R, Dong Y. Astrocyte and neuron intone through glutamate. Neurochem Res 2008; 33:2480.

150. Kirischuk S, Parpura V, Verkhratsky A. Sodium dynamics: Another key to astroglial excitability? Trends Neurosci 2012; 35:497-06.

151. Verkhratsky A, Noda M, Parpura V, et al. Sodium fluxes and astroglial function. Adv Exp Med Biol 2013; 961:295-05.

152. Benarroch EE. Astrocyte signaling and synaptic homeostasis I: Membrane channels, transporters, and receptors in astrocytes. Neurology 2016; 87:3.

153. Annunziato L, Boscia F, Pignataro G. Ionic transporter activity in astrocytes, microglia, and oligodendrocytes during brain ischemia. J Cereb Blood Flow Metab 2013; 33:969-82.

154. Verkhratsky A, Nedergaard M. Physiology of astroglia. Physiol Rev 2018; 98:239-89.

155. Fróes MM, Correia AHP, Garcia-Abreu J, et al. Gap-junctional coupling between neurons and astrocytes in primary central nervous system cultures. Proc Natl Acad Sci 1999; 96:7541-46.

156. Sontheimer H, Fernandez-Marques E, Ullrich N, et al. Astrocyte Na+ channels are required for maintenance of Na+/K(+)-ATPase activity. J Neurosci 1994; 14:2464-75.

157. Kinoshita PF, Leite JA, Orellana AMM, et al. The influence of Na+, K+-ATPase on glutamate signaling in neurodegenerative diseases and senescence. Front Physiol 2016; 7:195.

158. de Lores Arnaiz GR, Ordieres MGL. Brain Na+, K+-ATPase Activity in Aging and Disease Int J Biomed Sci 2014; 10:85-102.

159. Sweeney G, Klip A. Regulation of the Na+/K+-ATPase by insulin: Why and how? Mol Cell Biochem. 1998; 182:121-33.

160. Sodhi K, Maxwell K, Yan Y, et al. pNaKtide inhibits Na/K-ATPase reactive oxygen species amplification and attenuates adipogenesis. Sci Adv 2015; 1: e1500781.

161. Kinoshita PF, Yshii LM, Orellana AMM, et al. Alpha 2 Na+,K+-ATPase silencing induces loss of inflammatory response and ouabain protection in glial cells. Sci Rep 2017; 7:4894.

162. Vague P, Coste TC, M. F. Jannot, et al. Na+, K+-ATPase, and Diabetes. Exp Diabesity Res 2004; 5:37-50.

163. Tarnawa I, Bölcskei H, Kocsis P. Blockers of voltage-gated sodium channels for the treatment of central nervous system diseases. Recent Pat CNS Drug Discov 2007; 2:57-78.

164. Waszkielewicz AM, Gunia A, Szkaradek N, et al. Ion channels as drug targets in central nervous system disorders. Curr Med Chem 2013; 20: 1241-85.

165. Taylor CP. Sodium and Calcium Channel Blockers. In CNS Neuroprotection, Springer, Berlin, Heidelberg 2002; 209-44.

166. Ortner NJ, Striessnig J. L-type calcium channels as drug targets in CNS disorders. Channels 2016; 10:7-13.

167. Yang C, Hao Z, Zhang L, et al. Sodium channel blockers for neuroprotection in multiple sclerosis. Cochrane Database Syst Rev 2015; 10:CD010422.

168. Cornell-Bell AH, Finkbeiner SM, Cooper MS, et al. Glutamate induces calcium waves in cultured astrocytes: Long-range glial signaling. Science 1990; 247: 470-3.

169. Postnov DE, Koreshkov RN, Brazhe NA, et al. Dynamical patterns of calcium signaling in a functional model of neuron–astrocyte networks. J Biol Phys 2009; 35:425-45.

170. Nedergaard M. Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. Science 1994; 263:1768-71.

171. Navarrete M, Perea G, Maglio L, et al. Astrocyte calcium signal and gliotransmission in human brain tissue. Cerebral Cortex 2013; 23:1240-6.

172. Hayakawa K, Esposito E, Wang X, et al. Transfer of mitochondria from astrocytes to neurons after stroke. Nature 2016; 535:551-5.

173. Uchida S, Yamada S, Nagai K, et al. Brain pharmacokinetics and in vivo receptor binding of 1,4-dihydropyridine calcium channel antagonists. Life Sci 1997; 61:2083-90.

174. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm–A controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med 1983; 308:619-24.

175. Surmeier DJ. Calcium, ageing, and neuronal vulnerability in Parkinson's disease. Lancet 2007; 6:933-8.

176. Pasternak B, Svanström H, Nielsen NM, et al. Use of calcium channel blockers and Parkinson's disease. Am J Epidemiol 2012; 175:627-35.