EBioMedicine 69 (2021) 103474

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Review

Energy metabolism in childhood neurodevelopmental disorders

Oyarzábal A[a], Musokhranova U[a], Barros LF[b], García-Cazorla A[a,*]

[a] Neurometabolic Unit and Laboratory of Synaptic Metabolism. IPR, CIBERER (ISCIII) and MetabERN, Hospital Sant Joan de Déu, Barcelona, Spain
[b] Center for Scientific Studies – CECs, Valdivia 5110466, Chile

ARTICLE INFO

Article History:
Received 4 December 2020
Revised 30 January 2021
Accepted 18 June 2021
Available online 10 July 2021

Keywords:
Brain energy metabolism
Neurodevelopment
Inborn errors of energy metabolism
Rett syndrome
Autism

ABSTRACT

Whereas energy function in the aging brain and their related neurodegenerative diseases has been explored in some detail, there is limited knowledge about molecular mechanisms and brain networks of energy metabolism during infancy and childhood. In this review we describe current insights on physiological brain energetics at prenatal and neonatal stages, and in childhood. We then describe the main groups of inborn errors of energy metabolism affecting the brain. Of note, scarce basic neuroscience research in this field limits the opportunity for these disorders to provide paradigms of energy utilization during neurodevelopment. Finally, we report energy metabolism disturbances in well-known non-metabolic neurodevelopmental disorders. As energy metabolism is a fundamental biological function, brain energy utilization is likely altered in most neuropediatric diseases. Precise knowledge on mechanisms of brain energy disturbance will open the possibility of metabolic modulation therapies regardless of disease etiology.

1. The importance of energy metabolism in the brain

Information processing is expensive. The mammalian brain, gram per gram, consumes energy 10 times faster than the rest of the body, chiefly for the recovery of ion gradients, challenged by excitatory synaptic activity and action potentials [1,2]. In addition to high energy expenditure, the brain stands out for its unusual reliance on glucose, metabolic isolation by the blood-brain barrier, local recycling of metabolites, and marked division of metabolic labor between cell types. Neuronal signaling may account for most of the brain's energy budget, but astrocytes bear the brunt of the metabolic load, controlling the composition of the interstitial fluid, storing energy in the form of glycogen, supplying neurons with fuels and precursors for biosynthesis, and recycling neurotransmitters, oxidized scavengers, and other waste products [3]. In children, the brain demands even more energy, for growth and plasticity, and is relatively bigger, reaching up to 44% of the body's metabolic rate [4]. The adult brain is fueled almost exclusively by the oxidation of glucose, but other substrates become relevant when abundant in the circulation. During exercise, blood-borne lactate provides up to 25% of energy, with a corresponding reduction in fractional brain glucose consumption [5], whereas for every 1 mM increase in ketone bodies blood concentration, brain glucose consumption goes down by 10% [6,7], an effect of relevance during prolonged fasting and for the dietary treatment of seizures. In healthy neonates, ketone bodies supply about 10% of the energy consumed by the brain, a biochemical readiness that protects them against hypoglycemia [8].

Most glucose entering the brain is fully oxidized to CO_2, but the process is not homogeneous. In some regions a small but constant fraction of glucose metabolism stops at lactate, despite the presence of oxygen, a phenomenon termed aerobic glycolysis or Warburg Effect. Tonic aerobic glycolysis, which is actively studied in cancer [9], correlates with the expression of genes associated with synaptic formation and growth [10]. Noteworthy, these regions are also conspicuous for Alzheimer's beta-amyloid deposition [11]. A second instance of aerobic glycolysis is transient, lasting seconds to minutes, and is directly caused by local neural activity [12]. It is not obvious why lactate formation is preferred over full glucose oxidation, which yields 15 times more ATP. One hypothesis is that aerobic glycolysis serves to redistribute oxygen and fuel from astrocytes to neurons [13–16].

A related, but conceptually different question, is whether neurons are energized solely by glucose or co-energized by astrocytic lactate, as first proposed by Pellerin and Magistretti [17]. Thanks to technical advances in the last decade, including the measurement of glucose, lactate, NADH and other metabolites with high temporal resolution in individual cells *in vitro* and *in vivo*, it is now generally accepted that lactate produced by astrocytes serves to fuel neurons to some extent. The interested reader may like to peruse over the evidence in a CrossTalk debate and its associated correspondence [18,19]. More comprehensive reviews are also available although mostly focused on the adult brain [20,21]. In addition, it has emerged that lactate plays important signaling roles in brain tissue [22]. Much remains to

* Corresponding author.
E-mail address: agarcia@sjdhospitalbarcelona.org (G.-C. A).

https://doi.org/10.1016/j.ebiom.2021.103474

be elucidated. Neurons differ greatly in terms of synaptic input and firing regime, eg, excitatory versus inhibitory. Do they follow different fuelling strategies? Does a given neuron transit from one fuel to another at different stimulation levels? Are neurons located in brain regions characterized by tonic aerobic glycolysis and higher lactate levels fueled in a different manner? Future technical developments shall address the issues of neuronal subcompartments, ie, somatodendritic versus axonal, astrocytic subtypes, and the metabolic roles of oligodendrocytes and microglia.

In this article we aim to expose the current knowledge about both the physiological basis of brain energy metabolism and the disorders that disturb bioenergetics during neurodevelopment. To elaborate this review, we focus not only on inborn errors of energy metabolism but also on neurodevelopmental disorders in which brain energy dysfunction has been reported.

2. Energy metabolism and neurodevelopment: where are we now?

Whereas energy function in the aging brain and their related diseases has been explored in more detail, there is only limited knowledge about the molecular mechanisms and brain networks of energy metabolism at infancy and childhood. Despite its great interest, we only have scarce understanding on substrate utilization during neonatal and following periods, with most knowledge coming from studies in animal models such as rodents. Evidence demonstrates that neural development extends from the embryonic period through adolescence, in a sequence of events comparable among species [23]. While the differences between humans and rodent models have to be taken into account, analogous structures can be identified, and inferences regarding the maturation of specific brain structures or neural circuits in rodents and humans, can be made. Through this review, data from animal models (mouse and rat) or humans will be explained, clearly stating which is being analyzed. These models provide metabolic insight during the neonatal period, however, they need to be proven useful at reproducing human-specific development.

2.1. Brain energy during neonatal development

From an energy metabolism point of view, the main players to be taken into account in neurodevelopment are glucose, lactate and ketone bodies. On one side, glucose is metabolized through the glycolytic pathway to pyruvate, and further metabolized either to lactate or to Acetyl-CoA, entering the mitochondrial TCA (tricarboxylic acid) cycle. On the other side, lactate may be metabolized back to pyruvate, further processed in mitochondria, and ketone bodies are transported into the mitochondria for metabolism into Acetyl-CoA (Fig. 1).

Compared to the adult brain, the ratio of lactate and ketone bodies versus glucose utilization is higher in neonates. Taking data from animal models, in a 7 days postnatal rat glucose supports 63% of brain energy demands and ketone bodies provide 30% [24], while in fed non-ketotic adult rats glucose is the principal fuel of the brain. Lactate and other monocarboxylate (MCT) utilization by the fetal brain can be up to three-fold higher than the neonatal brain [25], highlighting the use of lactate during neurodevelopment.

The glucose/lactate utilization discrepancy is reflected in the expression of their blood-brain barrier (BBB) specific transporters. Neonate rat and mouse studies show a predominant expression of the monocarboxylate transporters [26], responsible for ketone body and lactate crossing, and a lowered expression of glucose transporters GLUT1 and GLUT3, responsible for the transport of glucose in the BBB and into neurons and glial cells [27,28]. The dynamic regulation of glucose transporters goes along with the expression of glycolytic enzymes, that change several fold between the neonate period and adult age in the studied models, such as PFK1 (Phosphofrucktokinase 1) or Hexokinase [24].

Ketone bodies (KBs) (acetoacetate, acetone and b-hydroxybutyrate) are an indispensable energy source in neurodevelopment at the fetal stage [29]. They provide acetoacetyl-CoA and acetyl-CoA for the synthesis of lipids, fatty acids and cholesterol, preferred over glucose for such biomolecules [30]. They are metabolized from medium and short fatty acids and imported into the brain through specific transporters such as MCT1. Regarding their energetic role, upon importation they are oxidized into acetyl-CoA, and enter into the TCA cycle. In suckling rodents, KB absorption and MCT1 expression is homogeneous throughout the brain, while in adult brains we find differences in their distribution. Interestingly, glucose and KB metabolism keep playing an important role through adult life. While glucose metabolic rate decreases in older adults, acetoacetate metabolism remains similar between the young and old, once again showing spatial differences across the brain. It should be noted that KBs are not only highly energetic but also precursors of cholesterol biosynthesis, which is over-represented in fetal metabolism compared to adults.

To what extent these pathways meet the energy needs of the neonatal brain was addressed by Ivanov et al. [31], who proved in neonatal hippocampal brain tissue preparations that synaptic function depended on oxidative metabolism; glycolysis alone not being able to meet its energetic needs. Simultaneously measuring field potentials, oxygen levels and NAD(*P*)*H* fluorescence, they proved that lactate not only sustained synaptic activity but enhanced it, together with oxygen utilization. Culturing hippocampal slices with 5 mM glucose and 5 mM lactate resulted in an increase of oxygen consumption and local field potentials (31% and 41% increase respectively), compared to activation with glucose alone. These results were further enhanced when lactate was the only substrate in the medium, confirming lactate as a neonatal brain fuel and implying that in neonates, lactate might be preferentially used over glucose when both substrates are present at equal concentrations [32].

Both lactate and KB metabolism converge in the mitochondria. Also, the complete oxidation of glucose requires the sequential action of glycolysis in the cytosol, followed by the mitochondrial decarboxylation of pyruvate mediated by PDH (pyruvate dehydrogenase), the incorporation of acetyl-CoA in the TCA cycle and the oxidation of reducing equivalents in the respiratory chain (Fig. 1). This review does not intend to cover mitochondrial function through development; however, its role has to be taken into consideration. Together with its bioenergetics function, mitochondria are a metabolic and signaling hub in the neuron. As a consequence of oxidative respiration, mitochondria produce reactive oxygen species (ROS). Under physiological circumstances, they act as signaling molecules that are required for synaptic plasticity [33] but they get severely deregulated upon mitochondrial insult. ROS overproduction can be found in many diseases [33] and, compared to other organs, the immature brain is especially vulnerable to ROS.

2.2. Beyond the neonatal period

After the neonatal period, brain lactate metabolism decreases through early infancy to childhood, while glucose uptake and metabolism rises. *In vivo* studies using hyperpolarized ^{13}C imaging reveal that the conversion rate of pyruvate to lactate on developing mouse brain models [34] decreases through development (Fig. 1b). In humans, following the early neonatal period, glucose consumption rapidly increases. Glucose PET scanning shows that, after the second year of life, when adult values are reached, glucose metabolic rates continue increasing. Then, in the third year of postnatal development, they exceed the adult values and sustain this rate until adolescence, when it gradually decays to adult values [35–37].

In the human neonatal brain, PET scans reveal early activation of subcortical areas such as the thalamus, brain stem, cerebellar vermis, amygdala, hippocampus, or cingulate cortex. These are evolutionarily preserved structures and related to neonate behavior as reflexes or

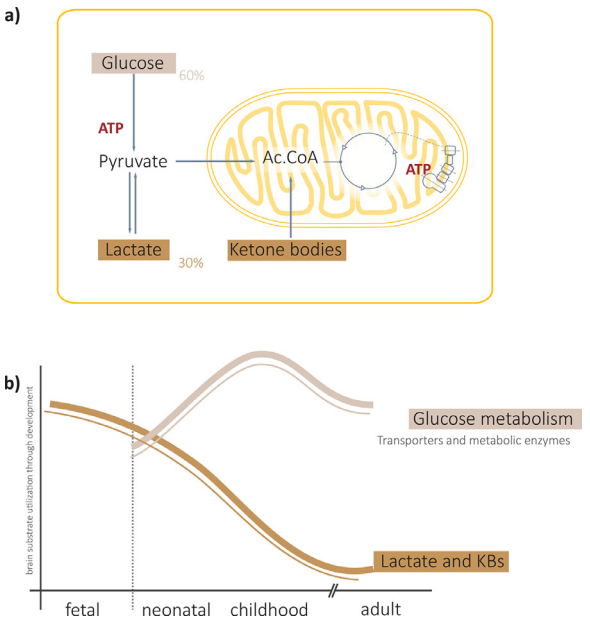

Fig. 1. *Energy metabolism during neurodevelopment: key molecules and their dynamics.* Glucose, lactate and ketone bodies (KBs) are key players in energy metabolism during neurodevelopment. (a) Basic pathways for energy production. In a 7-days postnatal rat, glucose supports around 60% of brain energy demands, and KBs support 30% (24). (b) Substrate utilization dynamics in the brain throughout development.

emotional processing and bonding. Later on, as functional complexity increases, maturation and glucose uptake augment in frontal eye fields, parietal cortex, basal ganglia and cerebellar cortex, ending in frontal cortex maturation [36].

Data on brain substrate utilization does not reveal the pathways the substrates undergo. Interestingly, an increase in oxygen consumption through development is delayed from glucose increase, suggesting the non-oxidative metabolism of glucose through this period. The oxygen-glucose index (OGI) has a theoretical maximum value of 6, meaning 1 molecule of glucose is fully oxidized with 6 molecules of O_2 to 6 CO_2 and water. This index drops below 6 when glucose is consumed by the brain but not oxidized, ie, non-oxidative metabolism of glucose despite oxygen availability (also referred to as aerobic glycolysis (AG) or Warbug effect). As a reference frame, in adult brains, AG accounts for 10–12% of total glucose metabolism, and is related to the most neotenous regions [10]. This ratio is increased in the developing brain by several fold [38], when synaptic growth is at its highest. While AG has been well documented in different contexts, such as cancer metabolism, as previously explained, its role on brain development remains to be elucidated. It has been proposed that this AG imbalance represents a way to sustain synaptogenesis as brain mass increases, but this has been ruled out as the only explanation since the theoretical increase in mass due to the AG ratio differs from the actual increase. Lactate production as the sole final fate of glucose was also discarded by performing a meta-analysis of lactate brain concentrations during childhood and noting that it did not peak as glucose did [39]. A combination of multiple routes appears to be the most plausible explanation. Other possible destinations for glucose carbon have to be taken into account, such as the pentose phosphate pathway (PPP) or biosynthetic precursors.

Although we have discussed the role of lactate in the neonatal brain, it is important not to obviate the role of glucose metabolism in brain development. Energetic metabolism of substrates such as lactate and KBs permit the utilization of glucose in alternative metabolic routes of crucial importance during neurodevelopment (Fig. 2). Basal PPP activity for instance accounts for 5–15% of glucose metabolism in the 7 day postnatal rat brain [40,41], showing a larger use of glucose in this pathway in the neonate compared to the adult [24]. Additionally, glucose is essential for a diverse number of key processes such as neurotransmitter homeostasis [19,42] or myelination [43] - a

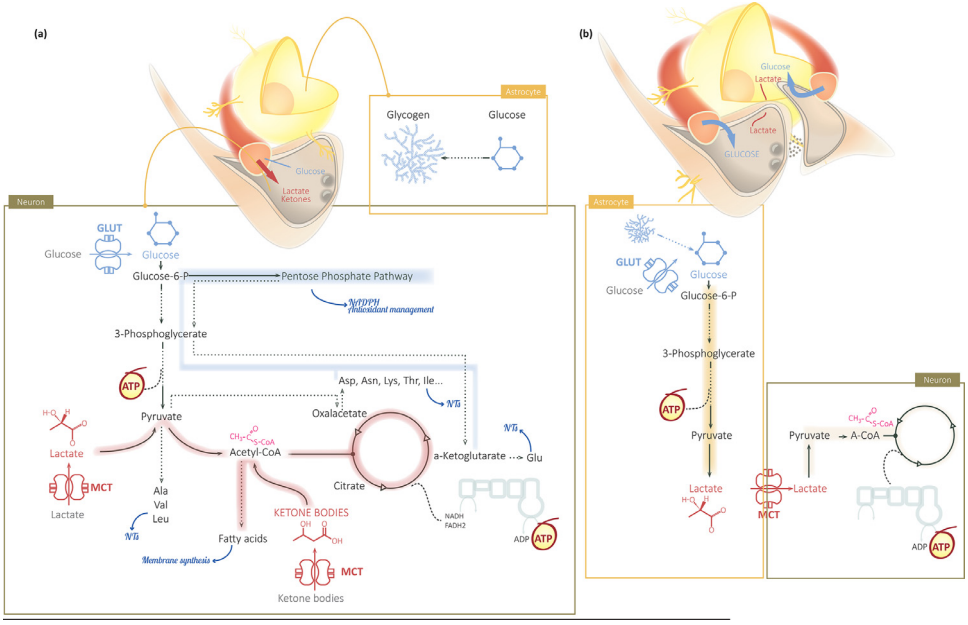

Fig. 2. *Perinatal to early infancy versus childhood to adolescence brain metabolism.* Only main variations between both development times are shown. (a) In the neonatal brain, lactate and ketone bodies (KBs) uptake versus glucose ratio is higher than in the adult brain. Upon importation of glucose into the neuron, it will be preferentially metabolized through the pentose phosphate pathway, generating both NADPH and precursors for the synthesis of nucleotides, as well as key element in the antioxidant defense of the cell. Glucose might also be further metabolized for the generation of oxalacetate, a-Ketoglutarate and pyruvate, all precursors of amino acids which also have specific roles as neurotransmitters (NTs), as is the synthesis of glutamate. Lactate and KBs are taken up by the cell at much higher rates than found in adults. They undergo metabolism for the production of Acetyl CoA, which can either enter the TCA cycle, producing NADH used by the mitochondrial electron transport chain for ATP synthesis, or for sterol synthesis, such as cholesterol, a key element for neurodevelopment signaling and essential component of membranes. KBs are preferentially used over lactate for fatty acid synthesis. (b) The astrocyte neuron lactate shuttle metabolism model is roughly represented for the adult brain metabolism scheme. Multichannel Transporters (MCRs) transport metabolites through membranes into the specified compartment.

high energy-demanding process used by oligodendrocytes that occurs throughout development as glucose consumption peaks. Glucose is also essential for oligodendrocyte precursor cell differentiation and migration [44], and mature oligodendrocytes rely on glycolysis for ATP production even in the presence of oxygen [45,46]. The switch from mitochondrial to glycolytic metabolism for ATP production might also respond to the necessity to reduce the production of ROS, a necessary by-product of respiratory chain activity [47]. Surprisingly, oligodendrocytes rely on lactate for myelin production and, as astrocytes, they supply lactate to the axon through MCT1 transporters [43]. We therefore find that both glucose and lactate are critical for brain function and development.

2.3. Common therapeutic strategies based on energy metabolism modulation

We have reviewed how energy metabolism is a crucial element of neurodevelopment. Given this, it can constitute not only a common pathway through different diseases (as will be further explained), but also a common therapeutic target. Besides their energetic functions, both lactate and KBs show neuroprotective roles [48,49], being candidates for common therapeutic development. Lactate produces a therapeutic effect in neonatal hypoxia-ischemia models [50,51]. It not only acts as an energetic substrate, but can also act directly on cell signaling through the activation of the HCAR1 receptor, potentiating angiogenesis [52] and neurogenesis in experimental intra-cerebral hemorrhage [53]. These results have been translated into clinical practice in adult traumatic brain-injured patients [54]. A similar effect has been demonstrated in neonatal hypoxia-ischemia rat models, where multiple sequential lactate injections after ischemic damage resulted in reduced brain damage and improved cognitive and sensorimotor deficits [50].

The therapeutic application of KBs is found in ketogenic diets (KD), used in the management of intractable epilepsy in children. Reported as a therapeutic option in 1921 [55], its antiepileptic mechanisms remain poorly understood. This therapeutic approximation is especially effective in the management of GLUT1-deficiency syndrome. This disease results from dominant mutations in *SLC2A1*, which encodes the facilitative transporter GLUT1, located in endothelial cells of the BBB and astrocytes and mediates the entrance of glucose into the brain. Deleterious mutations in *SLC2A1* reduce glucose availability to astrocytes and neurons, most commonly resulting in infancy-onset epilepsy, associated with movement disorders, cerebellar ataxia, and deceleration of head growth. Around 60% of the patients on KD become seizure-free, suggesting that 4-carbon KBs can compensate a glucose deficit. The results of KD in GLUT1 management [56] and other forms of intractable epilepsy and other conditions [57–59] exemplify the potential of energy metabolism as a therapeutic approach in neurodevelopmental diseases.

Defining alterations in energy metabolism and pathology in specific diseases, will be further reviewed. Understanding brain energy metabolism through development and its intricate relationship with neurodevelopment diseases sets the targets and time frames for therapeutic intervention [60,61] and proper development [62].

3. Monogenic disorders of energy metabolism

The importance of brain energy metabolism is completely reflected in the diseases that arise from primary defects of brain energy homeostasis [58,63]. These are genetic diseases of brain metabolism (inborn errors of metabolism: IEM) with symptoms due, at least in part, to a deficiency in energy production or utilization within the nervous system. In these IEM, other high-energy consumption organs (eg, muscle, heart, liver, eyes), are frequently involved. Most of them are pediatric-onset diseases. Therefore, they represent excellent models to study how energy is used in the neurodevelopmental brain. Functional tests measuring glucose, lactate, ketones and other energetic molecules (amino acids, organic acids, acylcarnitines) are useful diagnostic tools. According to a recently published simplified classification of IEM [64], these disorders could be divided into defects of membrane carriers of energetic molecules, cytoplasmic energy defects, and mitochondrial defects. Table 1 gives a global overview of these disorders. They encompass numerous diseases with diverse clinical manifestations from early-onset global encephalopathies to late-onset presentations, which may appear as movement disorders, stroke-like episodes, and neuromuscular signs amongst others.

Despite well-characterized clinical and biochemical descriptions, the cellular and molecular basis of brain energy impairment is still poorly understood in most of these IEM. As an example, in Glut1-deficiency syndrome, which is one of the most paradigmatic diseases, there is still insufficient knowledge regarding how energy is utilized on different nervous cells and compartments. However, ketogenic diet, an energy replacement therapy, shows important benefits for the patients [56].

Combined proton MRS (^{1}H MRS) and glucose metabolism PET could provide useful biomarkers of brain energetics in these rare disorders. However, there are only a few studies using this approach, and most reports in mitochondrial disorders have been performed in adults. In two children with congenital lactic acidosis, researchers found a massive increase of glycolysis to accommodate energy requirements in brain tissue [65]. Other than glucose, PET studies could also be used to trace pyruvate, lactate, and other energy molecules in the brain, leading to interesting data about the utilization of diverse fuels in the nervous system. However, these brain imaging techniques are not universally available and age-dependent control studies are scarce.

4. Energy metabolism in neurodevelopmental diseases

As reviewed so far, energy metabolism is essential for normal brain function and development, and can be both a common pathway of disease and - more importantly - a shared therapeutic strategy. Defects on brain metabolism result in neurodevelopmental diseases, as reviewed in the previous sections. Yet, remaining questions to be answered include: how is energy metabolism affected in monogenic neurodevelopmental diseases when it is not the primary cause of the disease? Can its modulation constitute a viable therapeutic strategy? As summarized in Table 1, in this section we review those neurodevelopmental diseases in which brain energy dysfunction has been reported in the scientific literature. First, we report on the studies of brain energy in neurological syndromes such as: (i)-autism spectrum and psychiatric disorders;-epileptic encephalopathies. Then we focused on specific genetic diseases: (ii) -Rett syndrome; -fragile-*X* syndrome; -Down syndrome, considered as the most common causes of intellectual disability.

4.1. Autism spectrum and psychiatric disorders

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that involves deficits in sociability and communication and increased restrictive and/or repetitive behavioral patterns.

Molecular pathways involved in ASD are as diverse as their etiology [66], including mitochondrial function, suspected to be involved in ASD development since 1985, when lactic acidosis was described in 5% of autistic patients [67]. Several studies support the linkage between mitochondria and ASD, which can be distributed into four categories [68]: (a) many genes coding for mitochondrial proteins have been described as ASD-risk genes, (b) studies in ASD patients' brain show impaired mitochondrial function, (c) blood studies point towards mitochondrial malfunctioning in ASD patients, and (d) abnormal mitochondrial function has been described in peripheral

Table 1

DISEASE	NEUROLOGICAL SYMPTOMS/TREATMENT	BIOCHEMICAL AND CELL BIOLOGY CHARACTERIZATION	BRAIN MAPPING
Inborn errors of metabolism primarily involving brain energy utilization			
Cell membrane carriers of energetic molecules			
GLUT1 *(SLC2A1)*	GLUT1 deficiency syndrome (GLUT1DS) is characterized by epilepsy, a complex movement disorder, and developmental delay. Variants of the classical form present with only one or two of the three items. Non-epileptic paroxysmal events: episodes of ataxia, dystonia, exercise induced.[1] Treatment: ketogenic diet	GLUT1 is a membrane glycosylated protein that transport glucose across the BBB and is also expressed in astrocytes (not in neurons). GLUT1DS causes a chronic neuroglycopenia which in turn produces the whole repertoire of clinical symptoms It should be suspected in any patient with a CSF glucose concentration < 2.5 mmol/l (normal >3.3 mmol/l). Values are age-specific and may vary considerably (range 0.9 - 2.9 mmol/l).[2]	PET studies: cortical hypometabolism in the mesial temporal regions and thalami; signal increase in the basal ganglia. Hypometabolism in bilateral thalami and increased uptake in bilateral lenticular nuclei.[3]
PAST-A (*SLC45A1*)	Intellectual disability, epilepsy and neuropsychiatric features. Facial dysmorphism. Stereotyped hand movements and behavioral problems including anxiety and autism.[4] There is no effective treatment	PAST-A is a proton-associated sugar transporter expressed in neurons. It links glucose transport to the gradient of protons allowing regulatory effects. Impaired uptake of glucose into neurons by this dysfunctional transporter results in the reported symptoms. Both plasma and CSF glucose are within normal limits	Brain MRI is normal. PET studies are not conclusive as diagnostic marker
MCT1 *(SLC16A1)*	Profound ketoacidosis after poor feeding and vomiting (van Hazzel, 2014). Homozygous mutations may cause severe developmental delay and abnormal brain MRI. Treatment: iv glucose or dextrose + bicarbonate	MCT1 is a protein that transport Lactate, Pyruvate and Ketones. MCT1 deficiency causes ketoacidosis due to ketone-body transport deficiency, necessary to maintain acid-base balance.	Homozygous mutations: White matter and sucortical U fibers involvement,. CC, Thalami and BBGG also Heterotopias.[5]
MCT12 (*SLC16A12*) Creatine transport	X-linked Intellectual disability, autistic features, behavioral disturbances, seizures and movement disorders (van Kamp, 2013). Treatment: high dose creatine, arginine, glycine and S-adenosylmethionine may offer some improvement	Creatine is involved in energy production and acts as an ATP shuttle from the inner mitochondria to the cytosol High urine creatine to creatinine ratio is a biomarker of the disease	Brain spectroscopy shows low creatine peak but a detailed study about anatomic areas and creatine quantification has not been published
Cytoplasmic energy defects			
Glycolysis and PPP defects	Most disorders present with myopathy. Those with prominent central nervous system have poor therapeutic options and are the following: **TPI deficiency:** movement disorders, spinal motor neuron involvement seizures and psychomotor delay. Haemolytic anemia There is no effective treatment. **PGK deficiency:** Haemolytic anemia, myopathy. ID and early-onset parkinsonism. **RPI deficiency:** leukoencephalopathy, seizures, spasticity, ataxia, neuroregression. **TKT deficiency**: developmental delay and short stature		
Glycogen defects Synthesis and catabolism	The neurological aspects of these disorders are due to complications of profound and/or recurrent hypoglycaemias. In the neonatal period and early infancy occipital and parieto-temporal areas are predominantly affected and may cause visual dysfunctions, seizures, acquired microcephaly and developmental delay.[6]		
Creatine defects	**AGAT deficiency:** non-syndromic ID with speech and language delay, microcephaly, hand stereotypies. **GAMT deficiency:** ID with speech and language delay, behavioral problems and epilepsy. Treatment: creatine supplementation in both defects. Ornithine in GAMT	Systemic and cerebral creatine deficiency AGAT: Low guanidinoacetate in urine GAMT: Elevated guanidinoacetate in urine Profound cerebral creatine deficiency *in vivo* brain MRS in all creatine defects.[7]	GAMT deficiency: globus pallidus involvement with T2 prolongation.
Mitochondrial defects			
General oxidative metabolism: energy components of the TCA cycle and Pyruvte metabolism that feed into OXPHOS			
Fatty acid oxidation	Most are treatable disorders. The neurological aspects of these disorders are due to complications of profound and/or recurrent hypoglycaemias but there are also some other symptoms depending on specific diseases: **LCHAD deficiency:** peripheral neuropathy; **Crotonase deficiency, *NADK2***: neurodegeneration; *ETFA, ETFB, ETFDH, CPTII:* brain malformations. **Riboflavin transport and metabolism defects** may impair beta-oxidation and produce ponto-bulbar palsy, deafness and peripheral neuropathy.		
Ketones metabolism	Most are treatable disorders. Other than the consequences of recurrent and/or profound hypoglycaemias, specific signs dependeing on every disease are the following: **Ketogenesis defects: - HMG-CoA lyase deficiency**: myelination abnormalities, cerebral atrophy and basal ganglia abnormalities. **Defects of KBs utilization or transport: succinyl-CoA:3-oxoacid CoA transferase (SCOT), mitochondrial acetoacetyl-CoA thiolase (T2) and monocarboxylate transporter 1 (MCT1):** severe ketoacidosis starting in early childhood, abnormalities in the basal ganglia in a number of patients with T2 deficiency. Some of these patients have presented with hypotonia, dystonia or chorea without any preceding episodes of acidosis. Abnormalities in the basal ganglia in a number of patients with T2 deficiency. Some of these patients have presented with hypotonia, dystonia or chorea without any preceding episodes of acidosis		
Pyruvate/lactate oxidation	**PC deficiency:** lactacidosis, ketosis, severe neonatal encephalopathy, episodic lactacidosis and ataxia, periventricular lesions. **PDH deficiency:** delayed development, hypotonia, seizures and ataxia, hyperpyruvicaemia, lactic acidaemia. Basal ganglia abnormalities. May respond to high thiamine doses and/or ketogenic diet. **Mitochondrial Pyruvate Carrier deficiency:** neonatal and mild progressive encephalopathy, hyperlactacidaemia with normal lacte/pyruvate ratio.		
Krebs cycle	**These defects include KDHC, SUCL, SDH, FH, ACO, MAS, and NAD(P)HX system repair defects.** Most of them cause encephalopathies with basal ganglia involvement (Leigh-like) and lactacidosis with specific organic acid profile. High doses of vitamin D3 (nicotinamide) has been suggested to be a treatment in NAD(P)HX system repair defects. Pyridoxine and serine in MAS deficiency.		

(*continued*)

Table ? 1 (*Continued*)

DISEASE	NEUROLOGICAL SYMPTOMS/TREATMENT	BIOCHEMICAL AND CELL BIOLOGY CHARACTERIZATION	BRAIN MAPPING
Respiratory chain and other mitochondrial functions			
OXPHOS subunits, assembly factors and electron carriers, mtDNA maintenance, mtDNA expression, mt aminoacyl tRNA synthetases, enzyme cofactors, mitochondrial homeostasis and quality control This is a large category of diseases that encompass about 300 genes[8]. About 200 genes have a primary role in OXPHOS biogenesis. Pathogenic mutations have been reported in all 37 mtDNA genes and all tRNA synthetases (19 genes). Only few are treatable so far: Vitamins, CoQ, Xenobiotic. Neurological manifestations are heterogeneous. Basal ganglia and cerebellar involvement are frequent. Most of them have a progressive character[9].			
DISEASE	**NEUROLOGICAL SYMPTOMS/TREATMENT**	**BIOCHEMICAL AND CELL BIOLOGY CHARACTERIZATION**	**BRAIN MAPPING**
Neurogenetic disorders in which brain energy dysfunction is a major mechanism of disease			
Rett syndrome (*MECP2*)	Regression in neurodevelopment between 6 and 18 months of age. Communicative ability and purposeful use of hands are lost, and stereotypies, autism signs, and seizure appear over time	Decrease in the OXPHOS complexes which results in ATP levels decrease, ROS production increase and an exaggerated redox responses both in cytosol and mitochondria has been shown. Abnormal mitochondrial morphology	Frontal lobe hypoperfusion, increased choline, and reduced NAA. However, glucose metabolism PET showed *hypermetabolism* of the frontal lobe (related to increased glutamate cycling in synapses).[10]
X-Fragile syndrome (*FMR1*)	Intellectual disability, diverse behavioral abnormalities, autistic signs, epilepsy	Respiratory chain complexes are up-regulated, elevated ROS production, decrease in ATP production, increased synthesis of TCA cycle and glycolytic enzymes	No energy brain mapping studies reported
Down syndrome	Intellectual disability, epilepsy and behavioral abnormalities may appear	Decrease of ATP production and increase in oxidative stress and altered mitochondrial dynamics.	Enhanced resting neuronal activity in cortical areas involved in reasoning, cognition, and speech This difference is confined to the dominant (left) hemisphere.[11]
Autism	Neurodevelopmental disorder that involves deficits in sociability and communication and increased restrictive and/or repetitive behavioral patterns	Impaired mitochondrial function: diverse respiratory chain abnormalities 1/3 of patients show elevated respiratory rates, approximately 200% of controls, for respiratory parameters associated with adenosine triphosphate production.[12]	PET studies: hypometabolism in parietal lobe, frontal premotor and eye-fields areas and amygdala. Rates increased in the posterior cingulate, occipital cortex, hippocampus and basal ganglia.[13]
Schizophrenia	Symptoms can include delusions, hallucinations, disorganized speech, trouble with thinking and lack of motivation	Decreased ATP production and increased oxidative stress. Increased lactate and decreased pH in schizophrenia brain.	PET studies: hypometabolism in the frontal lobe, anterior cingulate, superior temporal gyrus, amygdala and medial thalamic nuclei.[13]
Epileptic Encephalopathies	Other than epilepsy, neurodevelopmental delay motor symptoms and behavioral dysfunction are common	ATP depletion but transient ATP increase at the synaptic level, ROS increase. Oxidative damage, neurotransmitter uptake and release dysfunction.[14]	PET studies show different patterns of hypometabolism

Names of genes are in italics. ACO: Mitochondrial Aconitase deficiency; AGAT: Glycine Amidinotransferase Deficiency; BBB: blood brain barrier; GAMT: Guanidinoacetate Methyltransferase Deficiency; FH: Fumarase Deficiency; HMG-CoA: Mitochondrial 3-Hydroxy-3-Methylglutaryl-CoA; ID: intellectual disability; IV: intravenous; KBs: ketone bodies; KDHC: 2-Ketoglutarate Dehydrogenase Complex Deficiency; LCHAD: long-chain 3-hydroxyacil-CoA dehydrogenase deficiency. MAS: Malate-aspartate shuttle defects; MCT: monocarboxylate transporter; NAA: N-Acetylaspartate; NAD(P)HX system repair defects; NADK2: Dienoyl-CoA reductase; PC: pyruvate carboxylase deficiency; PDH: pyruvate deshydrogenase deficiency. PGK: Phosphoglycerate Kinase. PPP: pentose phosphate pathway; RPI: Ribose-5-Phosphate Isomerase; SDH: Succinate Dehydrogenase Deficiency; SUCL: Succinyl-CoA Ligase Deficiency Succinyl-CoA ligase deficiency; TKT: Transketolase deficiency; TPI: Triosephosphate Isomerase.

REFERENCES.

[1] Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, van Engelen BG, et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain. 2010 Mar;133(Pt 3):655–70.

[2] Leen WG, Wevers RA, Kamsteeg E-J, Scheffer H, Verbeek MM, Willemsen MA. Cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome: a systematic review. JAMA Neurol. 2013 Nov;70(11):1440–4.

[3] Natsume J, Ishihara N, Azuma Y, Nakata T, Takeuchi T, Tanaka M, et al. Lenticular nuclei to thalamic ratio on PET is useful for diagnosis of GLUT1 deficiency syndrome. Brain Dev. 2021 Jan;43(1):69–77.

[4] Srour M, Shimokawa N, Hamdan FF, Nassif C, Poulin C, Al Gazali L, et al. Dysfunction of the Cerebral Glucose Transporter SLC45A1 in Individuals with Intellectual Disability and Epilepsy. Am J Hum Genet. 2017 May;100(5):824–30.

[5] Nicolas-Jilwan M, Medlej R, Sulaiman RA, AlSayed M. The neuroimaging findings of monocarboxylate transporter 1 deficiency. Neuroradiology. 2020 Jul;62(7):891–4.

[6] Ferreira GC, McKenna MC. L-Carnitine and Acetyl-L-carnitine Roles and Neuroprotection in Developing Brain. Neurochem Res. 2017;42(6):1661–75.

[7] Fons C, Campistol J. Creatine Defects and Central Nervous System. Semin Pediatr Neurol. 2016 Nov;23(4):285–9.

[8] Frazier AE, Thorburn DR., Compton AG. Mitochondrial energy generation disorders: genes, mechanisms, and clues to pathology. J Biol Chem. 2019 Apr;294(14):5386–95.

[9] Saudubray J-M, Mochel F, Lamari F, Garcia-Cazorla A. Proposal for a simplified classification of IMD based on a pathophysiological approach: A practical guide for clinicians. J Inherit Metab Dis. 2019 Jul;42(4):706–27.

[10] Chugani HT. Positron Emission Tomography in Pediatric Neurodegenerative Disorders. Pediatr Neurol. 2019 Nov;100:12–25.

[11] Lengyel Z, Balogh E, Emri M, Szikszai E, Kollár J, Sikula J, et al. Pattern of increased cerebral FDG uptake in Down syndrome patients. Pediatr Neurol. 2006 Apr;34(4):270–5.

[12] Frye RE. Mitochondrial Dysfunction in Autism Spectrum Disorder: Unique Abnormalities and Targeted Treatments. Semin Pediatr Neurol. 2020 Oct;35:100,829.

[13] Mitelman SA, Bralet M-C, Mehmet Haznedar M, Hollander E, Shihabuddin L, Hazlett EA, et al. Positron emission tomography assessment of cerebral glucose metabolic rates in autism spectrum disorder and schizophrenia. Brain Imaging Behav. 2018 Apr;12(2):532–46.

[14] **Zhou Z**, Austin GL, Young LEA, Johnson LA, Sun R. **Mitochondrial** Metabolism in Major **Neurological Diseases**.Cells. 2018 Nov 23;7(12):229.

tissues and cells of autistic patients. These reports are complemented by studies in animal models, leading to the same conclusions. It has been proposed that systemic mitochondrial mutations can cause tissue-specific brain defects accompanied by regional neurophysiological alterations that result in autistic endophenotypes, as was demonstrated in a mouse strain bearing an mtDNA gene missense mutation [69].

Metabolic dysfunction can be either the primary cause (ie, IEM with features of ASD), or secondary contributions to precise ASD pathophysiology [70]. Different types of biomarkers (respiratory chain activities, lactate, pyruvate, alanine, lysine, carnitine, acyl carnitines) suggest the prevalence of abnormal mitochondrial function is much higher than the prevalence of classic mitochondrial disease, perhaps around 30−50% [71]. Additionally, studies in lymphoblastoid cell lines [72,73] derived from children show that one-third of patients present mitochondrial hyperactivity with elevated respiratory rates, approximately 200% that of controls, for respiratory parameters associated with adenosine triphosphate production [71].

One therapeutic strategy based on metabolic manipulation in ASDs is KD, but other strategies are being explored, such as supplementation with vitamins [74], N-acetylcysteine [75] or sulforaphane [76].

Regarding psychiatric disorders, we will focus on the three major psychiatric diseases: schizophrenia, bipolar disorder (BPD), and major depressive disorder (MDD). All three show differential expression in a substantial number of proteins related to energy metabolism (92 in SCZ, 95 in BPD, and 41 in MDD), five of which are common in the three diseases, such as citrate synthase [77], pointing towards impaired oxidative phosphorylation [78], increased glycolysis [79] and altered ROS-detoxification systems [80].

Schizophrenia is a developmental disorder that encompasses synaptic dysfunction. As in ASD, metabolic disturbances might be either the primary cause or secondary elements to the disease [81]. Moreover, metabolic studies in schizophrenia are hampered as most antipsychotics produce metabolic changes in patients [82]. Alterations in the electron transport chain activity, resulting in decreased ATP production and increased oxidative stress, have been reported [83−85] and these dysfunctions might be region- or cell-specific [81]. Additionally, multiple studies point to increased lactate and decreased pH in the schizophrenic brain. There is evidence to suggest that increased brain lactate may be directly related to diminished cognitive function [79] while decreased brain pH has been associated with increased emotional withdrawal [86]. Increased brain lactate seems to be driven by a high glycolysis rate and low TCA cycle and oxidative phosphorylation activity [87].

Psychiatric disorders continue to grow with a great impact on health, social and human rights [88]. Narrowing down the metabolic aspects of these diseases and investigating if they can constitute a therapeutic target is key for their proper management, as is the use of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in mood disorders, in particular for the treatment of depressive symptoms in unipolar and bipolar depression [89−91].

4.1.1. *Epilepsy and epileptic encephalopathies*

It is beyond the scope of this review to provide a detailed summary of early epileptic encephalopathies and energy metabolism disruption. Major evidence of the involvement of bioenergetics in the epileptic phenomenon comes from clinical practice: the use of KD as an alternative fuel supply and a membrane potential stabilizer. However, the connection between mitochondrial dysfunction, energy metabolism, and epilepsy in childhood has not been described in detail. Regardless of the etiology, seizure activity significantly decreases ATP levels in neurons, suggestive of energy depletion. Because neurons lack glycolytic capacities, the metabolic strain of post-seizure activity increases the demand for oxidative phosphorylation and may trigger an excess ROS and Ca^{2+} fluctuations (Table 1).

4.1.2. *RETT syndrome*

Rett syndrome (OMIM # 312,750) affects 1 in 10,000 people, usually due to *de novo* mutations in *MECP2*, located on the X chromosome. It is the second most common cause of intellectual disability in women and is characterized by a regression in neurodevelopment between 6 and 18 months of age. Communicative ability and purposeful use of hands are lost, and stereotypies, autism signs, and seizures appear over time [92,93]. Despite the great complexity of the disease, it seems clear that Rett syndrome is a disorder that arises from an imbalance between excitatory and inhibitory activity, and failure in the maturation of neural circuits, which remain in an immature state throughout development [94].

Prior to the description of *MECP*2 as the causative gene for Rett syndrome, it was questioned by the earliest studies to be a mitochondrial disease, as it shares many features with classic mitochondrial disorders (eg, early symptomatic debut, neurodevelopment delay, motor and intellectual regression, movement disorders), suggesting energy metabolism impairment [95]. An imbalance in the redox state has been described in fibroblasts from patients, which translates into oxidative damage in lipids and proteins, lowering of antioxidant defences (GSH) and morphological changes in the cell [96,97]. Furthermore, in murine models, a decrease in the OXPHOS complexes has been shown [98], resulting in a decrease in ATP levels, an increase in ROS production [99], and an exaggerated redox-response both in cytosol and mitochondria. Although a common pathway or element that explains mitochondrial dysfunction in Rett syndrome has not yet been found, there are many cases in which associated mitochondrial dysfunction is described as being responsible [100].

In spite of promising clinical trials [101], Rett syndrome lacks a specific treatment. Interestingly, correcting mitochondrial dysfunction is a potential therapeutic strategy [102]. Pharmacological stimulation of the mitochondrial serotonin receptor 5-HT7R effectively restores mitochondrial impairments in mouse models. Indeed, restoration of respiratory chain complexes together with the correction of mitochondrial ROS overproduction in different models of Rett syndrome, has resulted in a sustained phenotypic amelioration of the disease [99,103].

Setting the focus on mitochondria as a target for Rett syndrome could result in repurposing known drugs. Such is the case with metformin, used for decades in the treatment of type 2 diabetes [104−106], but whose mechanism of action has only been partially solved. Treatment of symptomatic Rett syndrome mouse models with 100 mg/kg metformin for 10 days resulted in an improvement of ATP brain levels and ROS production [107]. As concluded by the authors, “by improving brain mitochondrial dysfunction, metformin may rescue the neurological phenotype, thus representing an innovative and repurposable therapeutic strategy for Rett”.

4.1.3. *Fragile* X *syndrome*

Fragile *X* syndrome (FXS) (OMIM # 312,750) is the most frequent form of hereditary intellectual disability and genetic cause of autism. It associates epilepsy and behavioral abnormalities and is normally caused by a CGG triplet expansion within the X-located gene *FMR1*, resulting in the loss of expression of FMRP. FMRP is an mRNA-binding protein that controls different processes such as mRNA transport, splicing and translation or DNA damage response. This phenotype is accompanied by immature synapses and synaptic plasticity and excitotoxicity.

Besides the RNA-modulating function of FMRP, metabolic alterations have been described in FXS, suggesting a defect in mitochondrial physiology and oxidative phosphorylation [108]. These defects, including altered mitochondrial dynamics and increased oxidative stress, result in deficits in dendritic maturation, and have been described both in FXS mouse and *Drosophila* models [109,110]. Respiratory chain complexes are up-regulated in FXS mouse models [111], accounting for the elevated ROS production, but surprisingly, paired

to a decrease in ATP production. During early stages of development, ATP synthase subunit c accounts for a mitochondrial inner membrane leak, which favors glycolytic metabolism over oxidative phosphorylation. This leak is closed between embryonic days 11 and 13 in wild-type mouse cardiomyocites [112], when oxidative phosphorylation starts. As recently reported, such closure does not occur in FXS cells, resulting in the increased synthesis of TCA cycle and glycolytic flux-supporting enzymes. Pharmacological inhibition of the leakage results in recovery of the metabolic phenotype, favoring synapse maturation, and correction of autistic behaviors in FXS models [113].

Metabolic alterations have been described in plasma of both FXS models and patients. Plasmatic metabolites suggest a deregulation in glucose and lipid homeostasis, with a shifted metabolism towards the use of lipids and increased response to insulin stimulation [114]. Several studies report an increase in creatine and in BCAAs, asparagine and phosphocholine metabolism as well [114,115].

The role of glial metabolism in the pathophysiology of FXS is gaining relevance. Recent studies in *Drosophila* suggest FMRP has a role in insulin receptors activation in glia [116]. Although FXS-astrocytes mitochondria do not appear to have respiratory impairments, they show an increased ROS production [117], and extracellular vesicles in *Fmr1 KO* mouse models have been proved to be depleted mitochondrial components, specially those secreted from cortical astrocytes, endorsing the mitochondrial dysfunction in FXS pathophysiology [118].

Analogous with Rett syndrome, mitochondrial metabolism represents a potential target for the treatment of a generalized neurodevelopment disease. A study of nine FXS patients between the ages of 2 to 7 years old, treated with metformin, reported beneficial effects in language and behavior [119]. These results support the need for a controlled trial of metformin in young children with FXS to determine the effect of the treatment in a wider population.

4.1.4. Down syndrome

Down syndrome (DS) is the most common cause of intellectual disability, resulting from the presence of an either total or partial extra chromosome 21. Among other factors, the trisomy on this chromosome encompasses metabolic and mitochondrial alterations, that could be summarized by impaired glucose and lipid metabolism and defective mitochondrial activity, resulting in a decrease of ATP production and increase in oxidative stress [120]. Part of these alterations can be explained since key regulatory metabolic enzymes are encoded in chromosome 21, such as phosphofructokinase or cystathionine beta synthase. Studies in animal models suggest that abnormal glucose metabolism is already occurring during neurodevelopment, probably contributing to Down's brain function impairment.

Although not strictly falling into energy metabolism, brain lipid metabolism is also altered [121]. Reduced levels of glycerophosphoethanolamine and glycerophospholipid metabolism were observed in the DS prefrontal cortex. These results are complemented with the description of altered levels of sphingosine derivatives in DS fibroblasts [122].

4.2. Outstanding questions

There is still little knowledge about brain energy metabolism during neurodevelopment in both physiological and pathological conditions. Compared to advances in adult neurodegenerative disorders, energy dysfunction in neuropediatric diseases still represents a universe to be explored. However, energy homeostasis in neurodevelopmental diseases is probably a major pathophysiological feature. In fact, energy utilization is a fundamental biological mechanism carefully preserved across species and human evolution. Advanced in metabolomics, brain MRI spectroscopy and PET techniques will expand the knowledge of brain energy in neuropediatrics. Would intelligent integrative platforms using clinical, genetic, metabolic and pathophysiological data be robust enough to improve this knowledge? Whatever the methodology used, it is very likely that precise information on energy metabolism through neurodevelopment could provide new horizons in energy-based treatments regardless of the etiology of the neurological disease.

4.3. Search strategy and selection criteria

Data for this Review were identified by searches of PubMed mainly focused in the last 10 years (2011−2021). References from relevant articles were obtained using the search terms "neurodevelopment", "brain energy metabolism", "glycolysis", "oxidative phosphorylation", "lactate" "pyruvate", "monocarboxylate transporters", "ketone bodies", "inborn errors of metabolism", "mitochondrial disorders", "Rett syndrome", "X-fragile syndrome", "Autism", "Psychiatric diseases", "brain MRS", "Glucose PET".

5. Contributors

AO covered the issues of brain metabolism through neurodevelopment and neurodevelopmental diseases.

UM collaborated on the writing of neurodevelopmental diseases and energy metabolism.

LFB wrote the introductory aspects of this review, framing the importance of energy metabolism in brain function and setting the ground aspects for its development.

AGC conceived the whole manuscript structure and idea, supervised its contents and directly covered the monogenic disorders of energy metabolism.

All authors have read and approved the final version of this manuscript.

Declaration of Competing Interest

Dr Oyarzábal, MsC Musokhranova, Dr Barros and Dr García-Cazorla, have nothing to disclose

Acknowledgments

AGC is funded by Fondo de Investigación Sanitaria (FIS) P118/00111 (Instituto de Salud Carlos III: ISCIII and "Fondo Europeo de desarrollo regional" FEDER). We acknowledge the Spanish Patient Associations, "Mi Princesa Rett" and "Rettando al síndrome de Rett", for their continuous support to the "Synaptic Metabolism Laboratory" research at Sant Joan de Déu Hospital, Barcelona. The Centro de Estudios Científicos (CECs) is funded by the Chilean Government through the Centers of Excellence Basal Financing Program of ANID.

Refrences

[1] Erecińska M, Silver IA. Ions and energy in mammalian brain. Prog Neurobiol 1994;43(1):37–71 May.
[2] Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. J Cereb blood flow Metab 2001;21(10):1133–45 Off J Int Soc Cereb Blood Flow MetabOct.
[3] Weber B, Barros LF. The astrocyte: powerhouse and recycling center. Cold Spring Harb Perspect Biol 2015;7(12) Feb.
[4] Drunin. Basal metabolic rate in man. Joint FAO/WHO/UNU expert consultation on energy and protein requirements. Rome: WHO; 1981 http://www.fao.org/3/M2845E/m2845e00.htm.
[5] Rasmussen P, Wyss MT, Lundby C. Cerebral glucose and lactate consumption during cerebral activation by physical activity in humans. FASEB J 2011;25(9):2865–73 Off Publ Fed Am Soc Exp BiolSep.
[6] LaManna JC, Salem N, Puchowicz M, Erokwu B, Koppaka S, Flask C, et al. Ketones suppress brain glucose consumption. Adv Exp Med Biol 2009;645:301–6.
[7] Zhang Y, Kuang Y, Xu K, Harris D, Lee Z, LaManna J, et al. Ketosis proportionately spares glucose utilization in brain. J Cereb blood flow Metab 2013;33(8):1307–11 Off J Int Soc Cereb Blood Flow MetabAug.

[8] Vannucci RC, Vannucci SJ. Glucose metabolism in the developing brain. Semin Perinatol 2000;24(2):107–15 Apr.
[9] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 2009;324(5930):1029–33 May.
[10] Goyal MS, Hawrylycz M, Miller JA, Snyder AZ, Raichle ME. Aerobic glycolysis in the human brain is associated with development and neotenous gene expression. Cell Metab 2014;19(1):49–57.
[11] Bero AW, Yan P, Roh JH, Cirrito JR, Stewart FR, Raichle ME, et al. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. Nat Neurosci 2011;14(6):750–6 Jun.
[12] Fox PT, Raichle ME, Mintun MA, Dence C. Nonoxidative glucose consumption during focal physiologic neural activity. Science 1988;241(4864):462–4 Jul.
[13] Lerchundi R, Fernández-Moncada I, Contreras-Baeza Y, Sotelo-Hitschfeld T, Mächler P, Wyss MT, et al. NH4(+) triggers the release of astrocytic lactate via mitochondrial pyruvate shunting. Proc Natl Acad Sci U S A 2015;112(35):11090–5 Sep.
[14] San Martín A, Arce-Molina R, Galaz A, Pérez-Guerra G, Barros LF. Nanomolar nitric oxide concentrations quickly and reversibly modulate astrocytic energy metabolism. J Biol Chem 2017;292(22):9432–8 Jun.
[15] Fernández-Moncada I, Ruminot I, Robles-Maldonado D, Alegría K, Deitmer JW, Barros LF. Neuronal control of astrocytic respiration through a variant of the Crabtree effect. Proc Natl Acad Sci U S A 2018;115(7):1623–8 Feb.
[16] Barros LF, Ruminot I, San Martín A, Lerchundi R, Fernández-Moncada I, Baeza-Lehnert F. Aerobic glycolysis in the brain: warburg and crabtree contra pasteur. Neurochem Res 2020 Jan.
[17] Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci U S A 1994;91(22):10625–9 Oct.
[18] 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(3):347–50.
[19] Bak LK, Walls AB. CrossTalk opposing view: lack of evidence supporting an astrocyte-to-neuron lactate shuttle coupling neuronal activity to glucose utilisation in the brain. J Physiol 2018;596(3):351–3.
[20] Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci 2018;19(4):235–49 Apr.
[21] Dienel GA. Brain glucose metabolism: integration of energetics with function. Physiol Rev 2019;99(1):949–1045 Jan.
[22] Barros LF. Metabolic signaling by lactate in the brain. Trends Neurosci 2013;36(7):396–404 Jul.
[23] Rice D, Barone SJ. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect 2000;108(3):511–33 JunSuppl(Suppl.
[24] Brekke E, Morken TS, Sonnewald U. Glucose metabolism and astrocyte–neuron interactions in the neonatal brain. Neurochem Int 2015;82:33–41.
[25] Lust WD, Pundik S, Zechel J, Zhou Y, Buczek M, Selman WR. Changing metabolic and energy profiles in fetal, neonatal, and adult rat brain. Metab Brain Dis 2003;18(3):195–206.
[26] Rafiki A, Boulland JL, Halestrap AP, Ottersen OP, Bergersen L. Highly differential expression of the monocarboxylate transporters MCT2 and MCT4 in the developing rat brain. Neuroscience 2003;122(3):677–88.
[27] Pellerin L, Pellegri G, Bittar PG, Charnay Y, Bouras C, Martin JL, et al. Evidence supporting the existence of an activity-dependent astrocyte-neuron lactate shuttle. Dev Neurosci 1998;20(4–5):291–9.
[28] Kishimoto A, Takahashi-Iwanaga H, MW M, Iwanaga T. Differential expression of endothelial nutrient transporters (MCT1 and GLUT1) in the developing eyes of mice. Exp Eye Res 2016;153:170–7.
[29] Adam PA, Räihä N, Rahiala EL, Kekomäki M. Oxidation of glucose and D-B-OH-butyrate by the early human fetal brain. Acta Paediatr Scand 1975;64(1):17–24 Jan.
[30] Yeh YY, Sheehan PM. Preferential utilization of ketone bodies in the brain and lung of newborn rats. Fed Proc 1985;44(7):2352–8 Apr.
[31] Ivanov A, Mukhtarov M, Bregestovski P, Zilberter Y. Lactate Effectively Covers Energy Demands during Neuronal Network Activity in Neonatal Hippocampal Slices. Front Neuroenergetics 2011;3:2.
[32] Kasischke K. Lactate Fuels the Neonatal Brain. Front Neuroenergetics 2011;3:4.
[33] Beckhauser TF, Francis-Oliveira J, De Pasquale R. Reactive oxygen species: physiological and physiopathological effects on synaptic plasticity. J Exp Neurosci 2016;10(1):23–48 Suppl.
[34] Chen Y, Kim H, Bok R, Sukumar S, Mu X, Sheldon RA, et al. Pyruvate to lactate metabolic changes during neurodevelopment measured dynamically using hyperpolarized 13C imaging in juvenile murine brain. Dev Neurosci 2016;38(1):34–40.
[35] Chugani HT. A critical period of brain development: studies of cerebral glucose utilization with PET. Prev Med 1998;27(2):184–8 (Baltim).
[36] Chugani HT. Imaging brain metabolism in the newborn. J Child Neurol 2018;33(13):851–60.
[37] Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol 1987;22(4):487–97 Oct.
[38] Hyder F, Herman P, Bailey CJ, Møller A, Globinsky R, Fulbright RK, et al. Uniform distributions of glucose oxidation and oxygen extraction in gray matter of normal human brain: no evidence of regional differences of aerobic glycolysis. J Cereb blood flow Metab 2016;36(5):903–16 Off J Int Soc Cereb Blood Flow MetabMay.
[39] Benveniste H, Dienel G, Jacob Z, Lee H, Makaryus R, Gjedde A, et al. Trajectories of brain lactate and re-visited oxygen-glucose index calculations do not support elevated non-oxidative metabolism of glucose across childhood. Front Neurosci 2018;12:631.
[40] Brekke EMF, Morken TS, Widerøe M, Håberg AK, Brubakk AM, Sonnewald U. The pentose phosphate pathway and pyruvate carboxylation after neonatal hypoxic-ischemic brain injury. J Cereb blood flow Metab 2014;34(4):724–34 Off J Int Soc Cereb Blood Flow MetabApr.
[41] Morken TS, Brekke E, Håberg A, Widerøe M, Brubakk AM, Sonnewald U. Neuron-astrocyte interactions, pyruvate carboxylation and the pentose phosphate pathway in the neonatal rat brain. Neurochem Res 2014;39(3):556–69.
[42] Lund TM, Risa O, Sonnewald U, Schousboe A, Waagepetersen HS. Availability of neurotransmitter glutamate is diminished when beta-hydroxybutyrate replaces glucose in cultured neurons. J Neurochem 2009;110(1):80–91 Jul.
[43] Rinholm JE, Hamilton NB, Kessaris N, Richardson WD, Bergersen LH, Attwell D. Regulation of oligodendrocyte development and myelination by glucose and lactate. J Neurosci 2011;31(2):538–48.
[44] Yan H, Rivkees SA. Hypoglycemia influences oligodendrocyte development and myelin formation. Neuroreport 2006;17(1):55–9 Jan.
[45] Fünfschilling U, Jockusch WJ, Sivakumar N, Möbius W, Corthals K, Li S, et al. Critical time window of neuronal cholesterol synthesis during neurite outgrowth. J Neurosci 2012;32(22):7632–45 May.
[46] Rao VTS, Khan D, Cui QL, Fuh SC, Hossain S, Almazan G, et al. Distinct age and differentiation-state dependent metabolic profiles of oligodendrocytes under optimal and stress conditions. PLoS ONE 2017;12(8):e0182372.
[47] Rosko L, Smith VN, Yamazaki R, Huang JK. Oligodendrocyte bioenergetics in health and disease. Neurosci. 2019;25(4):334–43.
[48] Berthet C, Lei H, Thevenet J, Gruetter R, Magistretti PJ, Hirt L. Neuroprotective role of lactate after cerebral ischemia. J Cereb blood flow Metab 2009;29(11):1780–9 Off J Int Soc Cereb Blood Flow MetabNov.
[49] Lee BS, Woo DC, Woo CW, Kim KS. Exogenous β-hydroxybutyrate treatment and neuroprotection in a suckling rat model of hypoxic-ischemic encephalopathy. Dev Neurosci 2018;40(1):73–83.
[50] Roumes H, Dumont U, Sanchez S, Mazuel L, Blanc J, Raffard G, et al. Neuroprotective role of lactate in rat neonatal hypoxia-ischemia. J Cereb Blood Flow Metab 2020 0271678 × 2090835.
[51] Tassinari ID, Andrade MKG, Rosa LAda, Hoff MLM, Nunes RR, Vogt EL, et al. Lactate administration reduces brain injury and ameliorates behavioral outcomes following neonatal hypoxia-ischemia. Neuroscience 2020. doi: 10.1016/j.neuroscience.2020.09.006.
[52] Morland C, Andersson KA, Haugen ØP, Hadzic A, Kleppa L, Gille A, et al. Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. Nat Commun 2017;8:15557. May.
[53] Zhou J, Liu T, Guo H, Cui H, Li P, Feng D, et al. Lactate potentiates angiogenesis and neurogenesis in experimental intracerebral hemorrhage. Exp Mol Med 2018;50(7):1–12.
[54] Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensiv Care Med 2009;35(3):471–9 Mar.
[55] Wheless JW. History of the ketogenic diet. Epilepsia 2008;49(8):3–5 NovSuppl.
[56] Klepper J, Akman C, Armeno M, Auvin S, Cervenka M, Cross HJ, et al. Glut1 deficiency syndrome (Glut1DS): state of the art in 2020 and recommendations of the international Glut1DS study group. Epilepsia Open 2020;5(3):354–65 Sep.
[57] Barry D, Ellul S, Watters L, Lee D, Haluska R, White R. The ketogenic diet in disease and development. Int J Dev Neurosci 2018;68:53–8 [Internet]Available from http://www.sciencedirect.com/science/article/pii/S0736574818300960.
[58] Oyarzabal A, Marin-Valencia I. Synaptic energy metabolism and neuronal excitability, in sickness and health. J Inherit Metab Dis 2019;42(2):220–36.
[59] Kass HR, Winesett SP, Bessone SK, Turner Z, Kossoff EH. Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. Seizure 2016;35:83–7 Feb.
[60] Wachs TD, Georgieff M, Cusick S, McEwen BS. Issues in the timing of integrated early interventions: contributions from nutrition, neuroscience, and psychological research. Ann N Y Acad Sci 2014;1308(1):89–106.
[61] Georgieff MK, Brunette KE, Tran PV. Early life nutrition and neural plasticity. Dev Psychopathol 2015;27(2):411–23.
[62] Schwarzenberg SJ, Georgieff MK, COMMITTEE ON NUTRITION. Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health. Pediatrics 2018;141(2):e20173716.
[63] Frazier AE, Thorburn DR, Compton AG. Mitochondrial energy generation disorders: genes, mechanisms, and clues to pathology. J Biol Chem 2019;294(14):5386–95 Apr.
[64] Saudubray JM, Mochel F, Lamari F, Garcia-Cazorla A. Proposal for a simplified classification of IMD based on a pathophysiological approach: a practical guide for clinicians. J Inherit Metab Dis 2019;42(4):706–27 Jul.
[65] Duncan DB, Herholz K, Kugel H, Roth B, Ruitenbeek W, Heindel W, et al. Positron emission tomography and magnetic resonance spectroscopy of cerebral glycolysis in children with congenital lactic acidosis. Ann Neurol 1995;37(3):351–8 Mar.
[66] Kumar S, Reynolds K, Ji Y, Gu R, Rai S, Zhou CJ. Impaired neurodevelopmental pathways in autism spectrum disorder: a review of signaling mechanisms and crosstalk. J Neurodev Disord 2019;11(1):10.
[67] Coleman M, Blass JP. Autism and lactic acidosis. J Autism Dev Disord 1985;15(1):1–8 Mar.
[68] Cheng N, Rho JM, Masino SA. Metabolic dysfunction underlying autism spectrum disorder and potential treatment approaches. Front Mol Neurosci 2017;10:34.
[69] Yardeni T, Cristancho AG, McCoy AJ, Schaefer PM, McManus MJ, Marsh ED, et al. An mtDNA mutant mouse demonstrates that mitochondrial deficiency can result in autism endophenotypes. Proc Natl Acad Sci U S A 2021;118(6) Feb.

[70] Mierau SB, Neumeyer AM. Metabolic interventions in autism spectrum disorder. Neurobiol Dis 2019;132:104544.
[71] Frye RE. Mitochondrial dysfunction in autism spectrum disorder: unique abnormalities and targeted treatments. Semin Pediatr Neurol 2020;35:100829 Oct.
[72] Rose S, Bennuri SC, Wynne R, Melnyk S, James SJ, Frye RE. Mitochondrial and redox abnormalities in autism lymphoblastoid cells: a sibling control study. FASEB J 2017;31(3):904–9 Off Publ Fed Am Soc Exp BiolMar.
[73] Rose S, Frye RE, Slattery J, Wynne R, Tippett M, Melnyk S, et al. Oxidative stress induces mitochondrial dysfunction in a subset of autistic lymphoblastoid cell lines. Transl Psychiatry 2014;4(4):e377. Apr.
[74] Stewart PA, Hyman SL, Schmidt BL, Macklin EA, Reynolds A, Johnson CR, et al. Dietary supplementation in children with autism spectrum disorders: common, insufficient, and excessive. J Acad Nutr Diet 2015;115(8):1237–48 Aug.
[75] Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, Herzenberg LA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biol Psychiatry 2012;71(11):956–61 Jun.
[76] Singh K, Connors SL, Macklin EA, Smith KD, Fahey JW, Talalay P, et al. Sulforaphane treatment of autism spectrum disorder (ASD). Proc Natl Acad Sci U S A 2014;111(43):15550–5 Oct.
[77] Zuccoli GS, Saia-Cereda VM, Nascimento JM, Martins-de-Souza D. The energy metabolism dysfunction in psychiatric disorders postmortem brains: focus on proteomic evidence. Front Neurosci 2017;11:493.
[78] Maurer I, Zierz S, Möller H. Evidence for a mitochondrial oxidative phosphorylation defect in brains from patients with schizophrenia. Schizophr Res 2001;48(1):125–36 Mar.
[79] Rowland LM, Pradhan S, Korenic S, Wijtenburg SA, Hong LE, Edden RA, et al. Elevated brain lactate in schizophrenia: a 7 T magnetic resonance spectroscopy study. Transl Psychiatry 2016;6(11):e967. Nov.
[80] Martins-de-Souza D, Harris LW, Guest PC, Bahn S. The role of energy metabolism dysfunction and oxidative stress in schizophrenia revealed by proteomics. Antioxid Redox Signal 2011;15(7):2067–79 Oct.
[81] Sullivan CR, O'Donovan SM, McCullumsmith RE, Ramsey A. Defects in bioenergetic coupling in schizophrenia. Biol Psychiatry 2018;83(9):739–50.
[82] Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020;7(1):64–77 Jan.
[83] Dror N, Klein E, Karry R, Sheinkman A, Kirsh Z, Mazor M, et al. State-dependent alterations in mitochondrial complex I activity in platelets: a potential peripheral marker for schizophrenia. Mol Psychiatry 2002;7(9):995–1001.
[84] Mahadik SP, Evans D, Lal H. Oxidative stress and role of antioxidant and omega-3 essential fatty acid supplementation in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2001;25(3):463–93 Apr.
[85] Kuloglu M, Atmaca M, Tezcan E, Gecici O, Tunckol H, Ustundag B. Antioxidant enzyme activities and malondialdehyde levels in patients with obsessive-compulsive disorder. Neuropsychobiology 2002;46(1):27–32.
[86] Shioiri T, Someya T, Murashita J, Kato T, Hamakawa H, Fujii K, et al. Multiple regression analysis of relationship between frontal lobe phosphorus metabolism and clinical symptoms in patients with schizophrenia. Psychiatry Res 1997;76(2–3):113–22 Dec.
[87] Pruett BS, Meador-Woodruff JH. Evidence for altered energy metabolism, increased lactate, and decreased pH in schizophrenia brain: a focused review and meta-analysis of human postmortem and magnetic resonance spectroscopy studies. Schizophr Res 2020;223:29–42 Sep.
[88] Trautmann S, Rehm J, Wittchen H. The economic costs of mental disorders. EMBO Rep 2016;17(9):1245–9.
[89] Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry 2011 Dec;72(12):1577–84.
[90] Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry 2002;159(3):477–9 Mar.
[91] Bozzatello P, Brignolo E, De Grandi E, Bellino S. Supplementation with omega-3 fatty acids in psychiatric disorders: a review of literature data. J Clin Med 2016 Jul;5(8).
[92] Feldman D, Banerjee A, Sur M. Developmental dynamics of rett syndrome. Neural Plast 2016;2016:6154080.
[93] Leonard H, Cobb S, Downs J. Clinical and biological progress over 50 years in Rett syndrome. Nat Rev Neurol 2017;13(1):37–51 Jan.
[94] Banerjee A, Rikhye RV, Breton-Provencher V, Tang X, Li C, Li K, et al. Jointly reduced inhibition and excitation underlies circuit-wide changes in cortical processing in Rett syndrome. Proc Natl Acad Sci U S A 2016;113(46):E7287–96 Nov.
[95] Dotti MT, Manneschi L, Malandrini A, De Stefano N, Caznerale F, Federico A. Mitochondrial dysfunction in Rett syndrome. An ultrastructural and biochemical study. Brain Dev 1993;15(2):103–6.
[96] De Felice C, Ciccoli L, Leoncini S, Signorini C, Rossi M, Vannuccini L, et al. Systemic oxidative stress in classic Rett syndrome. Free Radic Biol Med 2009;47(4):440–8 Aug.
[97] Signorini C, Leoncini S, De Felice C, Pecorelli A, Meloni I, Ariani F, et al. Redox imbalance and morphological changes in skin fibroblasts in typical Rett syndrome. Oxid Med Cell Longev 2014;2014:195935.
[98] Can K, Menzfeld C, Rinne L, Rehling P, Kügler S, Golubiani G, et al. Neuronal redox-imbalance in rett syndrome affects mitochondria as well as cytosol, and is accompanied by intensified mitochondrial O_2 consumption and ROS release. Front Physiol 2019;10:479.
[99] Valenti D, de Bari L, Vigli D, Lacivita E, Leopoldo M, Laviola G, et al. Stimulation of the brain serotonin receptor 7 rescues mitochondrial dysfunction in female mice from two models of Rett syndrome. Neuropharmacology 2017;121:79–88.
[100] Panneman DM, Smeitink JA, Rodenburg RJ. Mining for mitochondrial mechanisms: linking known syndromes to mitochondrial function. Clin Genet 2018;93(5):943–51 May.
[101] Sandweiss AJ, Brandt VL, Zoghbi HY. Advances in understanding of Rett syndrome and MECP2 duplication syndrome: prospects for future therapies. Lancet Neurol 2020;19(8):689–98 Aug.
[102] Shulyakova N, Andreazza AC, Mills LR, Eubanks JH. Mitochondrial dysfunction in the pathogenesis of rett syndrome: implications for mitochondria-targeted therapies. Front Cell Neurosci 2017;11:58.
[103] De Filippis B, Nativio P, Fabbri A, Ricceri L, Adriani W, Lacivita E, et al. Pharmacological stimulation of the brain serotonin receptor 7 as a novel therapeutic approach for Rett syndrome. Neuropsychopharmacol 2014;39(11):2506–18 Off Publ Am Coll NeuropsychopharmacolOct.
[104] United Kingdom Prospective Diabetes Study (UKPDS). 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995;310(6972):83–8 Jan.
[105] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):854–65 Sep.
[106] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393–403 Feb.
[107] Zuliani I, Urbinati C, Valenti D, Quattrini MC, Medici V, Cosentino L, et al. The anti-diabetic drug metformin rescues aberrant mitochondrial activity and restrains oxidative stress in a female mouse model of rett syndrome. J Clin Med 2020;9(6):1669.
[108] Lumaban JG, Nelson DL. The Fragile X proteins Fmrp and Fxr2p cooperate to regulate glucose metabolism in mice. Hum Mol Genet 2015;24(8):2175–84.
[109] Shen M, Wang F, Li M, Sah N, Stockton ME, Tidei JJ, et al. Reduced mitochondrial fusion and Huntingtin levels contribute to impaired dendritic maturation and behavioral deficits in Fmr1-mutant mice. Nat Neurosci 2019;22(3):386–400 Mar.
[110] Weisz ED, Towheed A, Monyak RE, Toth MS, Wallace DC, Jongens TA. Loss of Drosophila FMRP leads to alterations in energy metabolism and mitochondrial function. Hum Mol Genet 2018;27(1):95–106 Jan.
[111] D'Antoni S, de Bari L, Valenti D, Borro M, Bonaccorso CM, Simmaco M, et al. Aberrant mitochondrial bioenergetics in the cerebral cortex of the Fmr1 knockout mouse model of fragile X syndrome. Biol Chem 2020;401(4):497–503.
[112] Hom JR, Quintanilla RA, Hoffman DL, de Mesy, Bentley KL, Molkentin JD, Sheu SS, et al. The permeability transition pore controls cardiac mitochondrial maturation and myocyte differentiation. Dev Cell 2011;21(3):469–78 Sep.
[113] Licznerski P, Park HA, Rolyan H, Chen R, Mnatsakanyan N, Miranda P, et al. ATP synthase c-subunit leak causes aberrant cellular metabolism in fragile X syndrome. Cell 2020;182(5):1170–85 e9.
[114] Leboucher A, Pisani DF, Martinez-Gili L, Chilloux J, Bermudez-Martin P, Van Dijck A, et al. The translational regulator FMRP controls lipid and glucose metabolism in mice and humans. Mol Metab 2019;21:22–35 Mar.
[115] Menzies C, Naz S, Patten D, Alquier T, Bennett BM, Lacoste B. Distinct basal metabolism in three mouse models of neurodevelopmental disorders. eNeuro 2021;8(2).
[116] Vita DJ, Meier CJ, Broadie K. Neuronal fragile X mental retardation protein activates glial insulin receptor mediated PDF-Tri neuron developmental clearance. Nat Commun 2021;12(1) Feb.
[117] Vandenberg GG, Dawson NJ, Head A, Scott GR, Scott AL. Astrocyte-mediated disruption of ROS homeostasis in Fragile X mouse model. Neurochem Int 2021;146:105036 Jun.
[118] Ha BG, Heo JY, Jang YJ, Park TS, Choi JY, Jang WY, et al. Depletion of mitochondrial components from extracellular vesicles secreted from astrocytes in a mouse model of fragile X syndrome. Int J Mol Sci 2021;22(1) Jan.
[119] Biag HMB, Potter LA, Wilkins V, Afzal S, Rosvall A, Salcedo-Arellano MJ, et al. Metformin treatment in young children with fragile X syndrome. Mol Genet genomic Med 2019;7(11):e956. Nov.
[120] Dierssen M, Fructuoso M, Martínez de, Lagrán M, Perluigi M, Barone E. Down syndrome is a metabolic disease: altered insulin signaling mediates peripheral and brain dysfunctions. Front Neurosci 2020;14:670.
[121] Yu Q, He Z, Zubkov D, Huang S, Kurochkin I, Yang X, et al. Lipidome alterations in human prefrontal cortex during development, aging, and cognitive disorders. Mol Psychiatry 2020;25(11):2952–69 Nov.
[122] Hwang S, Williams JF, Kneissig M, Lioudyno M, Rivera I, Helguera P, et al. Suppressing aneuploidy-associated phenotypes improves the fitness of trisomy 21 cells. Cell Rep 2019;29(8):2473–88 Nove5.