



## Review

## Energy metabolism in childhood neurodevelopmental disorders

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## 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 neuropsychiatric diseases. Precise knowledge on mechanisms of brain energy disturbance will open the possibility of metabolic modulation therapies regardless of disease etiology.

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## 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<sub>2</sub>, 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

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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 (Phosphofructokinase 1) or Hexokinase [24].

Ketone bodies (KBs) (acetoacetate, acetone and  $\beta$ -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.

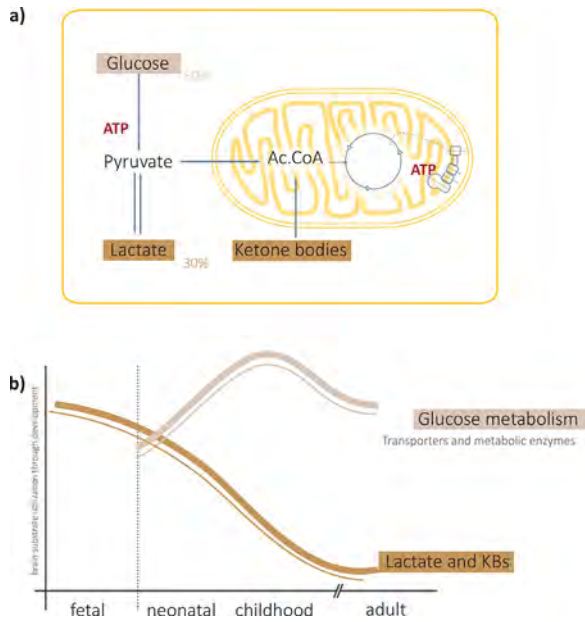
To what extent these pathways meet the energy needs of the neonatal brain was addressed by Ivanov et al. [31], who proved in neonatal hippocampal brain tissue preparations that synaptic function depended on oxidative metabolism; glycolysis alone not being able to meet its energetic needs. Simultaneously 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  $^{13}\text{C}$  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



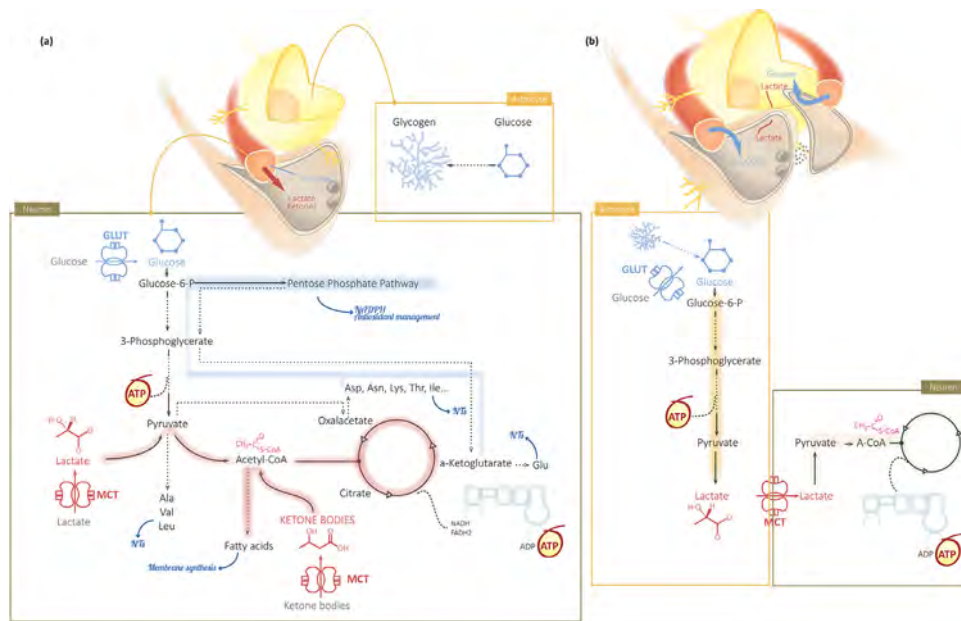
**Fig. 1.** Energy metabolism during neurodevelopment: key molecules and their dynamics. Glucose, lactate and ketone bodies (KBs) are key players in energy metabolism during neurodevelopment. (a) Basic pathways for energy production. In a 7-days postnatal rat, glucose supports around 60% of brain energy 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 Warburg effect). As a reference frame, in adult brains, AG accounts for 10–12% of total glucose metabolism, and is related to the most neonatal 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,  $\alpha$ -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 (MCTs) 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 ( $^1\text{H}$  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                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                |
| <b>Cell membrane carriers of energetic molecules</b>                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                |
| <b>GLUT1 (SLC2A1)</b>                                                                                          | 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. <sup>1</sup> 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). <sup>2</sup> | PET studies: cortical hypometabolism in the mesial temporal regions and thalamus; signal increase in the basal ganglia. Hypometabolism in bilateral thalamus and increased uptake in bilateral lenticular nuclei. <sup>3</sup> |
| <b>PAST-A (SLC45A1)</b>                                                                                        | Intellectual disability, epilepsy and neuropsychiatric features. Facial dysmorphism. Stereotyped hand movements and behavioral problems including anxiety and autism. <sup>4</sup> 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                                                                                                                                                       |
| <b>MCT1 (SLC16A1)</b>                                                                                          | 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 subcortical U fibers involvement, CC, Thalamus and BBGG also Heterotopias. <sup>5</sup>                                                                                                 |
| <b>MCT12 (SLC16A12)</b><br>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                                                                                        |
| <b>Cytoplasmic energy defects</b>                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                |
| Glycolysis and PPP defects                                                                                     | Most disorders present with myopathy. Those with prominent central nervous system have poor therapeutic options and are the following:<br><b>TPI deficiency:</b> movement disorders, spinal motor neuron involvement seizures and psychomotor delay. Haemolytic anemia There is no effective treatment. <b>PGK deficiency:</b> Haemolytic anemia, myopathy. ID and early-onset parkinsonism. <b>RPI deficiency:</b> leukoencephalopathy, seizures, spasticity, ataxia, neuroregression. <b>TKT deficiency:</b> developmental delay and short stature                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                |
| Glycogen defects<br>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. <sup>6</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                |
| Creatine defects                                                                                               | <b>AGAT deficiency:</b> non-syndromic ID with speech and language delay, microcephaly, hand stereotypies.<br><b>GAMT deficiency:</b> ID with speech and language delay, behavioral problems and epilepsy. Treatment: creatine supplementation in both defects. Ornithine in GAMT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Systemic and cerebral creatine deficiency<br>AGAT: Low guanidinoacetate in urine<br>GAMT: Elevated guanidinoacetate in urine<br>Profound cerebral creatine deficiency <i>in vivo</i> brain MRS in all creatine defects. <sup>7</sup>                                                                                                                                                                                                                | GAMT deficiency: globus pallidus involvement with T2 prolongation.                                                                                                                                                             |
| <b>Mitochondrial defects</b>                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                |
| General oxidative metabolism: energy components of the TCA cycle and Pyruvate 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: <b>LCHAD deficiency:</b> peripheral neuropathy; <b>Crotonase deficiency, NADK2:</b> neurodegeneration; <b>ETFA, ETFB, ETFDH, CPTII:</b> brain malformations. <b>Riboflavin transport and metabolism defects</b> 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 depending on every disease are the following:<br><b>Ketogenesis defects:</b> - <b>HMG-CoA lyase deficiency:</b> myelination abnormalities, cerebral atrophy and basal ganglia abnormalities.<br><b>Defects of KBs utilization or transport:</b> <b>succinyl-CoA:3-oxoacid CoA transferase (SCOT), mitochondrial acetoacetyl-CoA thiolase (T2) and monocarboxylate transporter 1 (MCT1):</b> 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                                                                                     | <b>PC deficiency:</b> lactacidosis, ketosis, severe neonatal encephalopathy, episodic lactacidosis and ataxia, periventricular lesions. <b>PDH deficiency:</b> delayed development, hypotonia, seizures and ataxia, hyperpyruvicaemia, lactic acidemia. Basal ganglia abnormalities. May respond to high thiamine doses and/or ketogenic diet. <b>Mitochondrial Pyruvate Carrier deficiency:</b> neonatal and mild progressive encephalopathy, hyperlactacidemia with normal lactate/pyruvate ratio.                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                |
| Krebs cycle                                                                                                    | <b>These defects include KDHC, SUCL, SDH, FH, ACO, MAS, and NAD(P)HX system repair defects.</b> 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 2 (Continued)

| DISEASE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | NEUROLOGICAL SYMPTOMS/TREATMENT                                                                                                                                                         | BIOCHEMICAL AND CELL BIOLOGY CHARACTERIZATION                                                                                                                                                                                                         | BRAIN MAPPING                                                                                                                                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Respiratory chain and other mitochondrial functions</b><br>OXPHOS subunits, assembly factors and electron carriers, mtDNA maintenance, mtDNA expression, mt aminoacyl tRNA synthetases, enzyme cofactors, mitochondrial homeostasis and quality control<br>This is a large category of diseases that encompass about 300 genes <sup>(8)</sup> . 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 <sup>(9)</sup> . |                                                                                                                                                                                         |                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                       |
| 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 ( <i>MECP2</i> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 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 <i>hypermotabolism</i> of the frontal lobe (related to increased glutamate cycling in synapses). <sup>10</sup> |
| X-Fragile syndrome ( <i>FMR1</i> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 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. <sup>11</sup>                                        |
| 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. <sup>12</sup> | 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. <sup>13</sup>          |
| 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. <sup>13</sup>                                                                      |
| 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. <sup>14</sup>                                                                                        | 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-hydroxyacyl-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 dehydrogenase deficiency. PGK: Phosphoglycerate Kinase. PPP: pentose phosphate pathway; RPL: Ribose-5-Phosphate Isomerase; SDH: Succinate Dehydrogenase Deficiency; SUCIL: Succinyl-CoA Ligase Deficiency Succinyl-CoA ligase deficiency; TKT: Transketolase deficiency; TPI: Triosephosphate Isomerase.

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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  $\text{Ca}^{2+}$  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 *MECP2* 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-HT<sub>7R</sub> 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 cardiomyocytes [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 neurodevelopmental 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 neuropsychiatric 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 neuropsychiatrics. 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-frangible 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.

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