Section A-Research paper

Acute metabolic consequences in tonic-clonic seizures

Mohamed Amer [1], Mohammed Ali Abdo [2], Asmaa Hosney Mohamed ElBahy [3], Ahmed Abdulsaboor [4]

[1] Lecturer of Pediatrics, Faculty of Medicine, Zagazig University
[2] Professor of Pediatrics, Faculty of Medicine, Zagazig University
[3] M.B; B.Ch.; Faculty of Medicine, Zagazig University
[4] Lecturer of Clinical Pathology, Faculty of Medicine, Zagazig University

Email: asmaahosney091@gmail.com

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Abstract

Background: The brain is a highly energy-dependent organ. At rest, it requires approximately 20% of oxygen and 25% of glucose relative to the rest of the body, although the brain comprises only 2–3% of total body weight. Neurons have an exceedingly high energy demand due to many cellular housekeeping functions such as synthesis and degradation of macromolecules, maintenance of cytoskeletal dynamics and axoplasmic transport, as well as other costly bioenergetic functions related to the high level of action potential signaling, synaptic activity, and plasticity changes. Lactate cannot passively diffuse across the blood brain barrier30, and since it cannot be directly utilized for energy production, it must be first transported via monocarboxylic transporters (MCTs) into cells, and then be subsequently converted enzymatically to pyruvate by lactate dehydrogenase (LDH) which exists in multiple isoforms – LDH1 being primarily expressed in neurons and LDH5 in astrocytes. However, the ANLS hypothesis is not without some controversy, as there is evidence that oxidative metabolism of lactate in neurons may not always be important for synaptic neurotransmission and the directionalities of lactate transport under different physiological conditions remain unclear. To truly appreciate the crucial role of metabolism in epilepsy and its pathophysiology, it is important to acknowledge the existence of bi- and multi-directional molecular interactions, which add layers of complexity to the many vicious cycles implicated thus far in the processes of epileptogenesis.

Keywords: Acute metabolism, tonic-clonic seizures

Introduction

The brain is a highly energy-dependent organ. At rest, it requires approximately 20% of oxygen and 25% of glucose relative to the rest of the body, although the brain comprises only 2–3% of total body weight. Neurons have an exceedingly high energy demand due to many cellular housekeeping functions such as synthesis and degradation of macromolecules, maintenance of cytoskeletal dynamics and axoplasmic transport, as well as other costly bioenergetic functions related to the high level of action potential signaling, synaptic activity, and plasticity changes **(1)**.

Although the brain is clearly energy demanding, it does not have an adequate energy reserve; hence, it must rely on a variety of exogenous energy sources to maintain normal function – mostly via transport of substrates through the blood-brain-barrier. That said, while astrocytes are known to store glycogen as a source of glucose-6-phosphate, a main substrate for glycolytic ATP production, this is wholly insufficient to meet the immediate energy needs of the brain and brain glycogen may act more as an emergency energy reserve and may also serve unique signaling functions between neurons and glia. Glucose is an obligate

source of energy for the brain , but other fuels such as lactate, ketone bodies and medium-chain fatty acids can be used when the availability of glucose is restricted **(2)**.

Astrocytes rely on both glycolysis and oxidative metabolism through the tricarboxylic acid (TCA) cycle to produce ATP. In contrast, neurons are much more dependent on the immediate availability of glucose that is extracted from the capillaries via glucose transporters (GLUT3, in particular). And while neuronal oxidative metabolism can generate much needed ATP for their high energy needs, neurons might maintain viability and long-term function by accessing some metabolic fuel from astrocytes. Specifically, there is some evidence that astrocytes and neurons control neurometabolic coupling by furnishing lactate according to the astrocyte-neuron lactate shuttle (ANLS) hypothesis **(3)**.

Lactate cannot passively diffuse across the blood brain barrier30, and since it cannot be directly utilized for energy production, it must be first transported via monocarboxylic transporters (MCTs) into cells, and then be subsequently converted enzymatically to pyruvate by lactate dehydrogenase (LDH) which exists in multiple isoforms – LDH1 being primarily expressed in neurons and LDH5 in astrocytes. However, the ANLS hypothesis is not without some controversy, as there is evidence that oxidative metabolism of lactate in neurons may not always be important for synaptic neurotransmission and the directionalities of lactate transport under different physiological conditions remain unclear **(4)**.

Moreover, when abnormally increased neuronal activity occurs during epileptic seizures, neurons may rely more on their own aerobic glycolysis than astrocyte-derived lactate. Nevertheless, to better understand cerebral blood flow, metabolism, and metabolic coupling among different cell types, it is important to examine the interdependent relationships between neurons, astrocytes and the microcirculation – elements that comprise at a unitary level the neurovascular unit. Finally, whether in neurons, glial cells or the vascular endothelium, mitochondria are the most important determinant of bioenergetics capacity, without which there can be no normal or even pathological function. Any compromise of mitochondrial function can induce dysregulation of intracellular calcium, increased oxidative stress, and ultimately apoptotic cell death **(5)**.

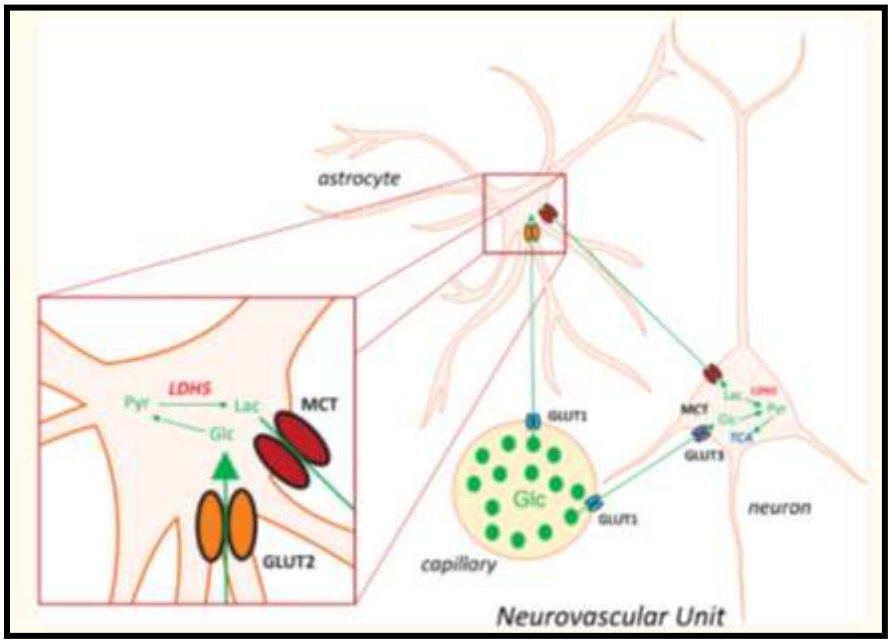

Figure (1): Astrocyte-Neuron Lactate Shuttle **(6)**.

Often neglected in the epilepsy field, glia clearly play a major role in seizure prevention, but also seizure genesis, controlling the ionic balance between intracellular and extracellular compartments, and modulating synaptic neurotransmission. During normal brain activity astrocytes play an important role in preventing neuronal hyperexcitability and seizures by buffering K^+ and by regulating glutamate uptake. Astrocytes can restore ionic and neurotransmitter homeostasis that is disrupted during seizure activity through various mechanisms, the most important of which is re-uptake of glutamate from the synaptic cleft and buffering of extracellular potassium through glial end-feet processes that link to the brain microvasculature **(7)**.

Importantly, in an in vitro stem cell model, re-uptake of glutamate into astrocytes triggered enhanced glycolysis, which in turn generated more pyruvate that was converted to lactate and subsequently transported to neurons via the ANLS. Moreover, it is increasingly recognized that astrocytes comprise large networks of highly inter-connected cells, mostly through gap junction channels (connexin43 and Cx30) which enable the bi-directional exchange of ions, nutritional metabolites, second messengers, amino acids, peptides, nucleotides, and even RNA. Hence, astrocytes are uniquely poised to modulate network activity – electrically and metabolically. In short, astrocytes, being able to use glycogen as fuel, play a critical role in maintaining energy metabolism but also excessive neuronal firing as seen during epileptic seizures. Indeed, there are growing lines of evidence implicating astrocytes in seizure genesis and epileptogenesis **(5)**.

Seizure-Induced Impairment of Metabolic Homeostasis

To truly appreciate the crucial role of metabolism in epilepsy and its pathophysiology, it is important to acknowledge the existence of bi- and multi-directional molecular interactions, which add layers of complexity to the many vicious cycles implicated thus far in the processes of epileptogenesis. Broadly stated, seizures by themselves cause an impairment in metabolic homeostasis, and a derailment of key metabolic and biochemical functions contributes to the increased likelihood of seizure generation. In this section, we discuss how epileptic seizures impact cellular metabolism. Acute seizures utilize glucose to fuel heightened energy demand and lead to the preferential formation of lactate rather than acetyl-coA **(4)**.

Given the availability of glucose, glycolytic flux increases during seizure activity but decreases during the interictal periods – changes which are believed to underlie the phenomena of ictal hypermetabolism and interictal hypometabolism, both long considered the metabolic hallmarks of human and experimental epilepsies. Whereas glycolysis is a less efficient process for ATP production, in comparison to the mitochondrial metabolism of acetyl-CoA, an increase in the glycolytic rate by a factor of 10 to 30 is adequate to generate immediate energy to sustain seizure activity. A shift toward glycolysis under aerobic conditions during seizures is supported by the increased production of lactate, mimicking the Warburg effect described in cancer cells which are intriguingly characterized by metabolic derangements mirrored in the epileptic brain **(8)**.

Increased ictal glucose metabolism may support plasticity processes in the brain, which include gliosis, neurogenesis, and axonal spouting. Mechanistically, glucose is not only used as a substrate for the generation of ATP, but is also a metabolic precursor for neurotransmitters and neuromodulators including acetylcholine, glutamate, GABA, D-serine, glycine, and D-aspartate. Together, alterations in key energy metabolites such as glucose, neurotransmitters, and neuromodulators are likely responsible for profound plasticity changes in the brain. A major metabolic consequence of increased ictal glycogen and glucose utilization is the formation of lactate from pyruvate through LDH. The hypothesis that seizure-induced lactate formation enables epileptic activity is supported by findings that LDH inhibitors provide robust anti-ictogenic effects. LDH inhibition is likely to interfere with glycolysis by limiting the availability of NAD^+ and supporting the oxidative metabolism of pyruvate in mitochondria **(9)**.

Given the alternative metabolic fates of glycolysis-derived pyruvate (lactate vs. mitochondrial oxidation), the impact of seizures on mitochondrial function is of paramount importance. Several enzymes involved in the mitochondrial TCA cycle, which converts pyruvate into carbon dioxide, are known to be compromised by acute seizures (e.g., status epilepticus or SE) or chronic seizure activity in epilepsy. Reduced activity of pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase, 2-oxoglutarate dehydrogenase, and aconitase, combine to reduce the flux of metabolites through the TCA cycle in the epileptic brain. In addition, the multimeric protein complexes of the electron transport chain (ETC) which enable oxidative phosphorylation – such as complex I – are known to be impaired in human temporal lobe epilepsy (TLE) and rodent models of epilepsy **(10)**.

High levels of oxygen and reactive oxygen species (ROS) are known to be detrimental to mitochondrial health. NADPH oxidase 2, also known as cytochrome b(558) subunit beta or Cytochrome b-245 heavy chain, is a superoxide-generating enzyme expressed in mitochondria and the plasma membrane, which has been shown to play a major role in the generation of SE-induced ROS. Seizure-induced increases in mitochondrial O_2 and H_2O_2 production can be attributed to higher substrate utilization and electron transfer

to O_2 during interictal periods, to an overload of calcium, and to the inhibition of ETC complexes, all of which combine to transfer electrons to oxygen also Seizures cause inactivation of the mitochondrial antioxidant superoxide dismutase 2 via decreased activity of Sirtuin 3 or altered activities of peroxide detoxification as additional mechanisms contributing to seizure-induced oxidative stress. The generation of ROS can result in the inhibition of complex I of the ETC, leading to ROS-induced ROS production, thus forming a pathologically regenerative cycle driving increased oxidative stress, which results in further free radical damage to cellular macromolecules – a major cause and consequence of extended seizure activity. Seizure-induced neuronal death can directly be attributed to oxidative stress and the formation of reactive aldehydes, hydroxyl radicals, and redox active iron, which induce damage to mitochondrial DNA, proteins, and lipids **(11)**.

In line with increased oxidative stress as a pathological hallmark of epilepsy, a depletion of the endogenous antioxidant glutathione and the formation of oxidized glutathione disulfide has been demonstrated in both human epilepsy and in rodent models of acquired epilepsy. Notwithstanding the above observations and our traditional understanding of the pathological effects of ROS, it is increasingly understood that ROS may possess signaling properties at low concentrations and can modulate GABAergic neurotransmission through both pre- and post-synaptic mechanisms **(12)**.

While ROS promote neurotoxicity, seizure-induced disruption of calcium homeostasis may also contribute to the detrimental effects of seizures. Excitotoxic neuronal death is primarily driven by excessive activation of N-methyl-D-aspartate (NMDA) receptors and the subsequent intraneuronal accumulation of toxic levels of calcium. This calcium overload in turn promotes the generation of ROS or reactive nitrogen species, which as outlined above compromise mitochondrial function, cause metabolic impairment and activate necrotic and apoptotic pathways, which are all calcium-dependent processes. Calcium imaging during an ictal event consistently demonstrates increased calcium influx in almost all neurons and astrocytes **(13)**.

Mitochondria are also crucially involved in the control of calcium homeostasis. Mitochondrial calcium homeostasis depends on mitochondrial calcium uniporter, rapid mitochondrial calcium uptake, and mitochondrial ryanodine receptors. Changes in calcium concentration in the mitochondrial matrix in turn regulate the activity of the mitochondrial ETC which is required for ATP production. Through this mechanism, an increase in seizure-induced calcium fluxes can directly compromise mitochondrial function **(14)**.

Energy metabolism in the discharge pathway is massively increased during seizures

During seizure activity, there is a greater increase in cerebral metabolic rate (CMR) than under any other circumstance. This is seen in measurements of oxygen consumption ($CMRO_2$) and glucose uptake and metabolism. It is also reflected in a marked increase in cerebral blood flow (CBF). The metabolic activation is confined to the brain regions involved in the seizure propagation; for example, during limbic seizures, such as those induced by kainic acid, the increases in CBF and $CMRO_2$ and the metabolic changes are confined to the limbic system. In contrast, generalized, global seizures cause metabolic activation to a varying degree in all brain regions. During seizures, there is commonly both an increase in arterial blood pressure and a marked local vasodilation, the latter partly due to local formation of nitric oxide and adenosine. The increase in CBF often exceeds the increase in $CMRO_2$ so that the oxygen content of the venous blood is increased. Provided that arterial blood pressure, arterial oxygenation and blood glucose concentration are maintained, this enhanced metabolism can also be maintained in excess of an hour of seizure activity **(15)**.

Energy metabolites decrease rapidly

Despite the sharp increase in oxygen and glucose supply to the brain, the massive increase in energy demand associated with the onset of seizure activity causes a rapid fall in brain energy metabolites. Tissue stores of glycogen and glucose are rapidly depleted, and concentrations of phosphocreatine and, to a lesser extent, ATP fall rapidly and transiently. Associated with the fall in nucleotide is a concomitant sharp rise in nucleosides, including adenosine and free bases, for example, hypoxanthine **(16)**.

Concentrations of lactate and certain amino acids change rapidly

Seizure activity is associated with a doubling or more of brain lactate, ammonia and alanine contents within 1 min. There is a modest fall in the intracellular pH at the same time. The lactate increase occurs in the absence of hypoxia and reflects the relatively greater increase in the glycolytic rate than in $CMRO_2$, the maximally activated pyruvic acid dehydrogenase being the rate-limiting step. Glutamate, aspartate and GABA concentrations initially remain constant, but if seizure activity is prolonged, glutamate and aspartate usually fall and glutamine and GABA rise **(17)**.

Second messengers change rapidly

There are dramatic changes in all of the second messengers that reflect increased release of neurotransmitters acting on metabotropic receptors within the first minute of seizure activity. Increases in cAMP are partly due to activation of α-adrenergic receptors. Increases in cGMP are partly due to formation of nitric oxide, following ionotropic glutamate receptor (NMDA) activation. Activation of glutamate, α_1-adrenergic or muscarinic metabotropic receptors causes phospholipase C (PLC) activation and phosphoinositide breakdown. The lipase activity results in the formation of diacylglycerol, which activates protein kinase C, and of inositol phosphate, which causes release of Ca^{2+} from nonmitochondrial stores. There is also a marked increase in intracellular Ca^{2+} concentration, $[Ca^{2+}]_i$, due to enhanced Ca^{2+} entry, through receptor and voltage-operated calcium ion channels **(18)**.

Free fatty acids and prostaglandins increase

The effects of these changes are to phosphorylate many enzymes, ion channels and cell membrane receptors and to directly activate calcium-dependent enzymes. Among the latter is phospholipase A_2, leading to the formation of free fatty acids, in particular arachidonic acid ,Primarily due to activation of phospholipases, free fatty acids are liberated during seizure activity. The greatest increase during seizures induced by electroshock or bicuculline is in the unsaturated fatty acid arachidonic acid, which acts as a precursor for various prostaglandins **(19)**.

Release of neurotransmitter amino acids is rapidly increased at the beginning of a seizure

The synaptic release of amino acid neurotransmitters was studied by in vivo microdialysis. In patients with epileptic foci in the temporal lobe, the extracellular hippocampal concentrations of glutamate and aspartate increase directly prior to or at the moment of seizure onset; the extracellular concentration of GABA rises with a slight delay in both the epileptic focus and the contralateral temporal lobe. A similar enhanced release of aspartate, glutamate and GABA is seen associated with the onset of seizures in chronically seizure-prone rodents, kindled rats or rats with spontaneous, recurrent seizures. It is more difficult to demonstrate an enhanced release of excitatory amino acids or GABA at the onset of acute, evoked seizures in rats, perhaps due to an optimally functioning amino acid-transporter system during these conditions **(20)**.

Seizures produce changes in gene expression and protein synthesis

There are also selective increases in the mRNAs for various trophic factors, such as nerve growth factor and neurotrophin 3. These changes have a longer latency of approximately 1 hr and a longer duration than the changes in the immediate early genes. With a longer latency still, there are increases in the expression of the genes encoding various peptide neurotransmitters and their precursors **(21)**.

Although the synthesis of some proteins, such as those mentioned above and the enzyme ornithine decarboxylase, is increased by seizures, the synthesis of most proteins is impaired during or after prolonged seizures in rats or newborn marmosets. When studied with labeled amino acid precursors and autoradiography, protein synthesis is impaired in those regions showing the greatest metabolic activation. The rate of protein synthesis depends on the cellular GDP:GTP ratio, with GDP increases being inhibitory **(22)**.

Positron emission tomography studies show ictal hypermetabolism and interictal hypometabolism

PET can be used to study the regional metabolism of the human brain during seizures and in the interictal period. Regional glucose uptake can be studied with fluorodeoxyglucose and oxygen extraction with oxygen. In partial epilepsy, enhanced metabolism is usually seen in the zone of seizure initiation during a seizure. Interictal studies in partial epilepsy commonly show a large zone of hypometabolism, which may

be more extensive than the presumed focal zone. Children with absence attacks show a marked diffuse increase in cerebral metabolism during the attack and normal interictal metabolism **(23)**.

Glycaemic Imbalances

The interplay between blood sugar levels and susceptibility to seizures is especially complex. Glucose is the main energy supply of the central nervous system. The human brain accounts for only 2% of body weight but consumes about 20% of glucose-derived energy of the whole body, and cerebral metabolic requests are likely much higher in paediatric age. This remarkable metabolic demand is due to both neuronal workflow (generation of action and postsynaptic potentials, maintenance of ion gradients, and resting potentials) and the biosynthesis of neurotransmitters by neurons and astrocytes. The grey matter utilizes a significantly greater amount of energy compared to the white matter, and the demand for glucose briskly increases with neuronal activation **(24)**.

Glycogen stores in the brain are tiny and limited to astrocytes, thus the brain is reliant on a continuous intake of glucose from the systemic circulation. Glucose movements within different compartments happen through glucose transporters (GLUTs). The entry within the central nervous system is mediated by the GLUT1 subtype, which allows facilitated diffusion through the blood–brain barrier. GLUT1 also mediates glucose uptake from brain extracellular fluid into glial cells. Instead, the GLUT3 subtype lets glucose flow into neurons and is much more efficient than GLUT1, insomuch as neurons are privileged with respect to glial cells in case of high metabolic demand **(25)**.

In human cells, energy can be produced from glucose by glycolysis in the cytosol and by oxidative phosphorylation (oxphos) in mitochondria. Intracellular glucose is initially metabolized to pyruvate by glycolysis, with no request for oxygen. Thereafter, pyruvate enters the mitochondrion and undergoes oxphos, which is much more efficient than glycolysis in terms of energy production; oxphos can only be performed in aerobiosis. Pyruvate is, instead, transformed to lactate in anaerobiosis, and energy production as ATP molecules is only obtained by low-efficiency glycolysis. The healthy brain may increase both glycolysis and oxphos in order to maximize the energy supply after acute activation **(26)**.

In epilepsy, there is a derailment of glucose catabolic pathways. Seizures greatly enhance the cerebral metabolic rate, increasing oxygen consumption, cerebral blood flow, and glucose uptake by neurons. Glucose metabolism is acutely shifted towards glycolysis and lactate production (ictal hypermetabolism), followed by a postictal decrease below baseline (postictal hypometabolism). Mitochondrial oxygen consumption also increases acutely, yet there is a net shift towards less efficient glycolysis despite aerobiotic conditions, reminiscent of the Warburg effect observed in cancer cells. Cerebral glucose availability may also be limited, because, in chronic epilepsy, GLUT transporters may be dysfunctional **(27)**.

On the other side, the disruption of mitochondrial oxphos could be involved in epileptogenesis. Experimental oxphos inhibition results in the destabilization of hippocampal membrane potentials and provokes epileptiform activity in initially healthy male rats. Neuronal excitability can also be directly affected by glycaemic levels. In the animal model, blood glucose concentrations positively correlate with susceptibility to seizures, and diabetes mellitus favours blood–brain barrier alterations during experimental epileptic seizures. In humans, both hyper- and hypoglycaemic conditions have been found to exacerbate seizures **(28)**.

As a matter of fact, glucose imbalances influence the brittle energy homeostasis of the brain. A disruption of energy availability affects the sodium–potassium pump and the resting state potential and increases intracellular calcium and reactive oxygen species that promote cell death. Hyperglycaemia can directly increase neuronal excitability acting on the ATP-sensitive potassium channels of hippocampal and neocortical neurons; hypoglycaemia depresses GABA levels enhancing excitatory transmission. Seizures usually improve with the control of glycaemic status in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), whereas fluctuations in blood glucose have been associated with drug-resistant epilepsy **(29)**.

Tonic-clonic seizures-related metabolic stress

Tonic-clonic seizures dramatically increase the energy demands of the brain and skeletal muscle. The changes in metabolites related to TCS show striking similarities to those found in extreme physical exertion, such as in athletic sprinting. A very important difference, however, is that an athlete has full mental control over voluntary movements allowing adjustments of physical activity to warning signals such as fatigue, pain, or shortness of breath, while the total loss of control during a TCS may lead to injuries such as vertebral fractures **(30)**.

During a seizure, the brain will use additional energy in a situation of apnea, whereas an athlete can adjust his breathing patterns to the metabolic needs. About 70% of the TCS in our study were accompanied by cyanosis and 97% received oxygen supplementation, which is part of our nursing standard after TCS. Finally, muscle contractions during physiological and voluntary activity are different from those during TCS, which may also partially explain, for example, the dramatic increase in lactate and other markers during a rather short time period of muscle activity **(31)**.

Assuming that the pattern of metabolic stress in TCS is to some extent comparable to that of maximum physical efforts, for example, during a sprint of 100-800 m, muscular ATP turnover increases 1000-fold. During the first seconds, most ATP is provided by the fast, 1-step reaction phosphagen system (creatine kinase, adenylate kinase, and AMP deaminase reactions), which leads to elevated phosphate and creatinine blood levels. The slower, multiple-step anaerobic glycolytic reactions take over as the main source of ATP production after 10-20 seconds. Lactate, the end product of anaerobic glycolysis, is released into the bloodstream. The lactate levels found in our study are as high as or higher than those after sprint races in athletes of various disciplines **(32)**.

Free protons from anaerobic glycolysis cause metabolic acidosis, which drives the AMP deaminase reaction of the purine nucleotide cycle, leading to increased ammonia and uric acid production, which are subject to hepatic metabolization and renal excretion, respectively. During intense exercise, liver and renal perfusion are reduced, further contributing to rising levels of ammonia and uric acid, as well as higher retention of creatinine and cystatin c that we found. Unlike physiological exercise, the level of metabolic acidosis in TCS may be aggravated by respiratory acidosis **(33)**.

The transient hyperammonemia seen in TCS is similar to or exceeding the one observed in bouts of maximum effort exercise of similar length to a TCS. Apart from skeletal muscle, lactate and ammonia may be released to a lesser extent from the brain itself. Experimental data in rats show that cerebral ammonia and lactate production is increased in seizures. Transient hyperuricemia after TCS is rarely analyzed in clinical practice. Rising uric acid levels have been observed not only in the muscular exercise but also in the seizing rat brain, indicating that both organ systems are potential contributors. High postictal uric acid can lead to acute renal failure independently from rhabdomyolysis. The changes in electrolytes and osmolality are likely to reflect fluid shifts caused by the metabolic changes discussed above **(30)**.

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