

Role of Minerals in Childhood Epilepsy

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Abstract

Background: The cornerstone of brain activity is changes in membrane voltage caused by ion fluxes through voltage and transmitter-gated channels. Therefore, electrochemical gradients across the membrane determine the direction and driving force for ion flow, which in turn establishes synaptic transmission and signal propagation parameters. Numerous methods create ion concentration gradients and specialised transporter proteins are among them. However, ionic fluxes via channels can alter transmembrane gradients during times of increased brain activity, which is projected to have an impact on the characteristics of ongoing synaptic transmission. Both healthy and unhealthy brain processes involve activity-induced alterations to ion concentration gradients. Patients with epilepsy display a variety of altered trace elements, electrolytes, and free radical scavenging enzyme statuses. Minerals play an important role in regulating ion concentration gradients through their various biological actions.

Objectives: This review would contribute in increasing understanding of the role of minerals in childhood epilepsy and the different mechanisms by which different types of minerals modulate seizures in children.

Conclusion: The serum level of various trace elements and heavy metals influences the impact of epilepsy. In infantile epilepsy, high calcium concentrations in epileptic neurons remain elevated during both the acute damage and chronic epilepsy phases, and they play a role in the maintenance of spontaneous recurrent seizures.

Keywords: Epilepsy; Minerals; Ion channels; Heavy metals.

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Introduction

The term "epilepsy" refers to a group of chronic seizure disorders that are characterized by sudden, transient episodes of seizures accompanied by loss of consciousness or other mental disturbances, often but not always accompanied by a distinctive body movement (convulsion), and occasionally by automatic hyperactivity. Seizures are caused by irregular neural discharges (Sharma et al., 2019).

Epileptic seizures affect 1-2% of the general population and 4% of children. The poorer standards of diet and public hygiene, the higher chance of brain injury, cerebral infection, or other symptomatic cerebral problems, contribute to the higher prevalence in developing countries. Age has an impact on seizure frequency. The incidence rate is highest in the first year of life (100 per 100,000) and then declines to about 20 cases per 100,000 per year by adolescence. It is estimated that 0.5-0.8% of children have epilepsy, which is a diverse set of illnesses(Saad, 2014).

Role of Minerals in epilepsy

(A) Macro-minerals:

1. Calcium:

Calcium is a crucial factor for neurons to operate normally and at the neuromuscular

junction. Since the cell is already depolarized, the excitability of neurons increases the extracellular glutamate content, reflecting a rise in intracellular neuronal calcium. This further depolarizes the cell and, in circumstances of excessive neuronal activation, might harm or kill the neuron. The increased Ca^{+2} concentration in the epileptic neurons persists during both the acute injury phase and the chronic epilepsy phase. and contributes to the maintenance of spontaneous recurrent seizures.(Zang et al., 2018)

It can change the recycling of GABAA receptors, which may be a plausible mechanism for how Ca^{+2} affects neuronal excitability. The patients with epilepsy were found to have reduced calcium levels. According to the notion, hypomagnesemia reduces the amount of parathyroid hormone produced or secreted, which results in a membrane condition where neurons are more excitable. This is assumed to be the mechanism through which low calcium levels (hypocalcemia) cause seizures to occur(Xu & Tang, 2018).

2. Potassium:

In mice, spontaneous and recurring seizures are linked to mutations in the genes encoding sodium/hydrogen exchange protein, potassium, and calcium channels. Mutations in the potassium and

sodium channel genes have been linked to rare Mendelian epilepsy disorders in humans. Inward-rectifying potassium ion channels have been shown to have a unique role in epilepsy, and contemporary anticonvulsant drug discovery efforts acknowledge them as a novel class of biological targets for treating epilepsy (Auzmendi et al., 2021).

It is generally known that there is a correlation between extracellular potassium ion concentration and neuronal excitability. When extracellular potassium concentrations are above 5 mM or below 2 mM, neurons become hyperexcitable. As a result of minute variations in the inward rectifying channel, the extracellular potassium ion concentration may be significantly affected both during and after neuronal excitation (Bjurulf et al., 2020).

The frequency of the K allele differs from population to population and around the world. People from many nations or geographical places may exhibit heterogeneity. Ion channel gene mutations have been linked to a growing number of illnesses and syndromes known as channelopathies (Kodama et al., 2019).

Kir channels play a crucial role in maintaining potassium homeostasis, linking the metabolic condition of the cell with membrane excitability, and

controlling the resting membrane potential. In the brain, Kir4.0 is a potent inward rectifier. It is mostly expressed in glia, where it may be involved in potassium buffering. K, which is referred to as an allele for seizure susceptibility, can also influence the emergence of common seizure types (Akyüz et al., 2018).

2.1. Hypokalemia and Hyperkalemia

Contrary to other electrolyte disorders, seizures do not happen when hypokalemia or hyperkalemia are present. The cardiovascular and neuromuscular systems are primarily affected by changes in extracellular potassium serum levels. Therefore, before CNS symptoms manifest, a severe potassium imbalance may cause lethal arrhythmias or muscle paralysis (Jacoby, 2020).

3. Sodium:

Both a genetic sodium channel gene mutation and an acquired insult to healthy sodium channels can result in epilepsy; both mechanisms were discussed here. Numerous families with inherited epilepsy have been shown to have sodium channel mutations (Catterall, 2017). Families with GEFS+ (generalized epilepsy with febrile seizures plus) have identified sodium channel alterations in one GABA receptor

subunit, SCN1A, SCN2A, and SCN1B. (GABRG2)(**Musto et al., 2020**).

The SCN1B gene was damaged in the first family in which a GEFS+ mutation was discovered. The C121W mutation replaces a tryptophan (W) with a highly conserved cysteine residue (C) in amino acid 121. The change slows down channel inactivation and makes it unable to regulate channel gating because it destroys a disulfide bridge in the extracellular loop of the 1 subunit(**Menezes et al., 2020**).

A cluster of sodium channel subunits on chromosome 2q24–33 was connected to additional families with GEFS+. SCN1A's S4 voltage sensor area is where the majority of mutations are found. Numerous functional flaws were discovered, among other things, a rise in INaP, a gain-of-function mutation's telltale sign. Increased INaP may facilitate seizures (**Tidball et al., 2020**). Among the additional pathophysiological anomalies linked to GEFS+ are changing in the voltage dependence of activation or inactivation. Mutations, such as those that appear to decrease sodium channel excitability, can result in epilepsy (such as a positive shift in the voltage dependence of activation and a sluggish recovery from inactivation) (**Ridley et al., 2017**).

Dravet syndrome, or severe myoclonic epilepsy of infancy (SMEI), is a second epilepsy disease involving sodium channel abnormalities. During the first year of life, affected children first experience febrile seizures, which are then followed by uncontrollable seizures and cognitive impairment. SCN1A mutations, the majority of which are frameshift or missense, are present in about one-third of children with SMEI, particularly in the pore region (S5–S6). Intractable infantile epilepsy with generalized tonic-clonic seizures is a newer SMEI form (ICEGTC)(**Barker et al., 2017**).

Increased INaP is present in some ICEGTC mutants, but not all. Last but not least, benign familial neonatal-infantile seizures (BFNIS), a novel condition, have been identified. It is characterized by seizures that stop by the age of one and are not linked to any long-term neurological consequences. Mutated channels displayed aberrant gating characteristics in transfected neocortical neurons in primary culture, which were predisposed to increased sodium current via a positive shift of the inactivation curve or a negative shift of the activation curve, enhancing neuronal excitability. Unlike SCN1A mutations, which can result in either an increase or a decrease in sodium channel

function, these mutations always result in gain-of-function(Li et al., 2018).

3.1. Hyponatremia

Hyponatremia is defined as a serum sodium level of less than 135 mEq/L, whereas severe hyponatremia is defined as a level of less than 125 mEq/L(Adrogué et al., 2022).

There is a strong correlation between the severity of cerebral edoema and the neurological symptoms of hyponatremia, which are more often caused by chronic than acute hyponatremia. Even when their serum sodium level is below 125 mEq/L, almost 50% of people with persistent hyponatremia are asymptomatic. Until their serum sodium level falls below 120 mEq/L, these patients hardly ever have symptoms, which are frequently connected to values of 110 mEq/L or less. Because of their higher brain-to-skull ratio, children are more likely than adults to have symptomatic hyponatremia. When the plasma sodium concentration falls below 115 mEq/L, seizures, which are frequently generalised tonic-clonic and may be triggered by severe and rapidly increasing hyponatremia, usually begin(Fibbi et al., 2021).

3.2. Hypernatremia

Hypernatremia is defined as a plasma sodium concentration in the serum that is greater than 145 mEq/L. The degree of CNS impairment is mostly connected with the rate at which serum sodium increases in hypernatremia. Acute hypernatremia causes shrinkage in brain volume (particularly in babies) and hyperosmolality, which when combined leads to encephalopathy because CNS cells' synaptic structure and function are changed. On the other hand, the likelihood of brain shrinkage and consequent neurological symptoms is reduced in persistent hypernatremia situations(Seay et al., 2020).

As much as 170 mEq/L of sodium can be added to the blood slowly and gradually, and this is typically well tolerated. Severe neurologic symptoms are the major signs and symptoms of hypernatremia, and they often appear after an abrupt rise in plasma sodium concentration to >158-160 mEq/L (i.e., within hours). Values >180 mEq/L are more frequently found in adults than in children and are linked to a high death risk. Seizures are normally not present in newborns with hypernatremia, but they can happen in cases of unintentional sodium loading or vigorous rehydration(Shirazy et al., 2020).

4. Magnesium:

Numerous in vitro investigations have demonstrated that reduced magnesium concentrations are linked to seizures because dietary magnesium deficiencies can lower seizure thresholds. Magnesium aids in the body's absorption of vitamin B6, a cofactor necessary for the production of GABA. The ability of magnesium to block N-methyl-D-aspartate (NMDA) receptors may also contribute to its anti-seizure effects (Kirkland et al., 2018).

Because it can block the excitatory calcium influx through the NMDA receptor, magnesium has the potential to modulate seizure activity. Low magnesium levels have also been demonstrated to make seizures more common in people with refractory epilepsy, which is the key risk factor for the emergence of sudden unexpected death in epilepsy (SUDEP). Additionally, it was observed that a lack of magnesium lowers seizure thresholds in animals with epilepsy. Additionally, recurrent seizures can be stopped and prevented with the use of the efficient medicinal drug magnesium sulphate (Doboszewska et al., 2022).

(B) Microminerals:

1. Selenium:

Selenium plays a role in a detoxifying enzyme, glutathione peroxidase. This

element has been demonstrated to have a positive biological function in various aspects of human health. Oxidative stress and the generation of reactive oxygen species are strongly implicated in several neurologic disorders, including seizure disorders. According to research conducted over the last three decades, selenium offers protection against cell damage brought on by reactive oxygen species. Selenium-requiring processes are involved in normal maintenance of cell function (Yuan et al., 2021).

According to measurements of local enzyme activity, catalase and glutathione peroxidase levels at the iron epileptic focus were comparatively low at the epileptic focus. The peroxidation of membrane lipids caused by an increase in free radical production or a decrease in the activities of antioxidant defence mechanisms has been considered a significant element in seizure control. The subsequent reduction in glutathione peroxidase activity that would follow further selenium depletion would increase lipid peroxidation susceptibility, leading to membrane and neural cell damage. Selenium functions as a potent neuroprotective compound by inducing the expression of selenoproteins, which are principally involved in the regulation of oxidative status and antioxidant defence (Al Omairiet al., 2022).

Antioxidant defence mechanisms prevent further oxidative damage from spreading to biomolecules like lipids, lipoproteins, and deoxyribonucleic acid. They also safeguard prostacyclin synthesis and maintain the integrity of membranes. Additionally, selenium deficiency affects the rate of certain neurotransmitters (monoamines). In experimental rats fed low-selenium diets, noradrenaline and 5-hydroxy-3-indoleacetic acid turnover increased, whereas dopamine and serotonin turnover decreased. Recurrent seizures may also result from the overactivation of glutamate receptors caused by selenium deficiency, which makes antiepileptic medications that act through GABAergic receptors ineffective. (Ahmad et al., 2022).

2. Iron:

According to several reports, the development of the seizure condition may be influenced by the level of certain trace elements, such as iron and chromium. From the following processes, iron deficiency and iron deficiency anemia may play a significant role in the development of seizures : 1. A change in the metabolism of the inhibitory neurotransmitter GABA; 2. A change in the metabolism of neurons; 3. 4. A decrease in the brain's oxygenation and energy metabolism. 5. A decrease in the activity of several enzymes, such as

monoamine and aldehyde oxidases. Numerous neurotransmitters require iron for proper metabolism, and lower levels of monoamine and aldehyde oxidases result in iron deficiency anemia(Prakash et al., 2019).

3. Manganese

The trace element manganese is required for the proper growth and operation of the central nervous system. According to reports, manganese is necessary for the action of the enzyme glutamine synthetase, which turns glutamate into glutamine. However, a manganese deficiency results in glutamate accumulation, which then triggers seizures(Zhu et al., 2022).

4. Zinc and Copper

Micronutrients like zinc and copper are crucial for many cellular processes. They are concentrated in the hippocampus, olfactory bulb, and hypothalamus, among other parts of the brain. In places like glutamatergic neurons, these trace elements build up in the synaptic vesicles and are co-released with neurotransmitters during typical synaptic events. Several theories suggest that epilepsy may be linked to changes in zinc homeostasis in the brain(Eissa et al., 2020).

Zinc's role in seizure activity is debatable because it contributes to the production and operation of the inhibitory

neurotransmitter GABA on the one hand and inhibits GABA on the other, which promotes seizure activity. Reactive oxygen species (ROS) and free radicals, which can harm or kill neurons, are produced when there is an excess of zinc in the body. Additionally, hypozincemia stimulates the NMDA receptors, which may be crucial in the development of epileptic discharge. (Bakri et al., 2022).

The important trace element copper functions as a cofactor for several enzymes. It prevents the disruption of Na, K homeostasis caused by Mg ATPase and Na, K ATPase enzymes, which ultimately delays the start of epileptic convulsions. Previously, it was understood that excessive amounts of copper can harm biological systems by oxidation, including the peroxidation of lipids or other macromolecules, which aids in the development of epilepsy (Sarkar et al., 2019).

(C) Heavy metals:

1. Aluminum

The hippocampus is the main site for aluminium buildup. Imaging reveals the presence of both extracellular and glial cell-based aluminium. The presence of numerous structures resembling spherulite in the visual cortex of the occipital lobe is connected to the presence of densely

mineralized tissue in the same area. Although lumogallion staining was unable to confirm the co-localization of aluminium and spherulites, the tissues likewise had substantial levels of aluminium (Mold et al., 2019).

Several brain donors in a recent study showing high aluminium levels in autism brain tissue had epilepsy. It has been demonstrated that aluminium excess in renal transplant patients is a risk factor for epileptic seizures. Additionally, it has been observed that people with epilepsy have greater blood levels of aluminum (Meng et al., 2019).

2. Mercury

Hyperintense brain lesions in children who were mercury-intoxicated as well as mercury intoxications brought on by mercury-containing skin cream have both previously been documented. It has been shown that severe mercury intoxications can coincide with increased neuron-specific enolase (NSE) (Suraev et al., 2022).

Patients with inorganic mercury intoxications exhibit general symptoms such as: itching, erythema, renal tubular failure, and nephrotic syndrome, as well as neurological and psychological symptoms like weariness, sleeplessness, weakness, and acrodynia. Magnetic

resonance imaging (MRI) scans reveal hyperintense lesions in the putamen, globus pallidus, and cerebral white matter. Axon degeneration, cell death, and neuron loss are all effects of mercury and its metabolic byproducts. The T2-weighted MRI sequences show these demyelinating effects. NSE concentrations may be high (Geier et al., 2018; Kornilova, 2021).

3. Lead:

Lead can disrupt a child's developing nervous system and brain. Memory, intelligence quotient, focus, and attention can all be negatively impacted by an increase in blood lead levels of more than 10 micrograms per deciliter. According to numerous studies, high blood lead levels in pregnant women, even in small amounts, might increase the amount of this element in the foetus' blood, which could cause sensory, motor, and cognitive deficits (Noori et al., 2021).

The most common nerve diseases are seizures, which can all be brought on by exposure to certain poisons like lead. The seizures, known as febrile convulsions, occur when a youngster is unwell and has a high fever (Bakhtiari et al., 2020).

An earlier study revealed that there was no discernible difference between neonates with fever and seizures (febrile convulsions) and those without seizures in

terms of blood lead levels. According to a study, blood lead levels exceeding 10 g/dL can impair short-term memory, reduce intelligence quotient (IQ), and make it difficult to concentrate. In that study, patients' blood lead levels did not correlate with their age or fever (Subbarao et al., 2019).

A previous study has linked child seizures and high blood lead levels (Naranjo et al., 2020). A previous study discovered that neurological abnormalities can be brought on by trace quantities of lead (less than 10 g/dL). But according to a different study, lead can cross the blood-brain barrier in children. They emphasise that lead can cause seizures, comas, and death in children (Lange & Fortner, 2020).

Summary

The severity of epilepsy is influenced by the serum concentrations of certain trace elements, electrolytes, and heavy metals, including selenium, iron, manganese, zinc, and copper (aluminium and mercury). The high calcium concentration in the epileptic neurons in children with epilepsy remains increased both during the acute damage phase and the chronic epilepsy phase, and it contributes to the maintenance of spontaneous recurrent seizures. High levels and mutations in Na⁺ and K⁺ channels are associated with epileptic

episodes. However, low levels of trace elements and magnesium are major inducers of epilepsy due to the loss of inhibitory neurotransmitters and other

biological actions. Also, intoxication with heavy metals has been associated with epilepsy.

Table 1: Summarizing role of minerals in childhood epilepsy

Mineral	Consequence	Reference
Calcium	Hypocalcemia may lead to seizures by altering GABAA receptor recycling, which alters neuronal excitability.	Xu, & Tang, 2018
Potassium	Subtle variations in the inward rectifying channel alter extra-cellular potassium ion concentration, making neurons hyperexcitable, especially when extracellular potassium is above 5 mM or below 2 mM.	Bjurulf et al., 2020
Sodium	GEFS+ mutations may disrupting disulfide bridge in the extracellular loop of the $\beta 1$ subunit, slowing channel inactivation and leading to increased INaP, facilitating seizures.	Tidball et al., 2020
Magnesium	Lower magnesium leads to a decrease in seizure threshold with loss of anti-seizure effect due to decreased inhibition of NMDA receptors.	Kirkland et al., 2018
Selenium	In selenium depletion, the further lowering of glutathione peroxidase activity causes higher susceptibility to lipid peroxidation with resulting neuronal cell and membrane damage. Also, there is increased dopamine and serotonin turnover and decreased noradrenalin and 5-hydroxy-3-indoleacetic acid turnover, which induce seizures.	Ahmad et al., 2022
Iron	Iron deficiency causes the decrease of GABA inhibitory neurotransmitters, a change in neuron metabolism, and impairment in oxygenation and energy metabolism of the brain, causing seizures.	Prakash et al., 2019
Manganese	Manganese deficiency causes an accumulation of glutamate, leading to the generation of seizures.	Zhu et al., 2022
Zinc and Copper	Hypo-zincemia activates NMDA receptors, which may induce epileptic discharge. High copper concentrations cause oxidative damage, which contributes to epilepsy.	Bakri et al., 2022 Sarkar et al., 2019
Aluminum	Aluminum accumulation in the glial cells of the hippocampus alters the neural function, causing epilepsy.	Mold et al., 2019
Mercury	Mercury intoxications cause elevated neuron-specific enolase which induces seizures.	Suraev et al., 2022
Lead	Lead can pass from the blood-brain barrier in children, causing impairment in normal metabolic function. Thus, high levels of blood lead levels are associated with seizures.	Lange, & Fortner, 2020

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