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HYPERKALEMIA AND BRAIN FUNCTION

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ABSTRACT

Hyperkalemia is an increase in blood potassium (K+) that can affect multiple organs, including the functioning of the brain. K+ remains stable between meals due to K+ release primarily from muscle and liver cells, while it decreases with renal excretion and sequestration from muscle cells. K+ resides almost entirely within cells and is absorbed in the small intestine. Increases in this electrolyte can occur with impaired renal excretion or cellular dysfunction. Hyperkalemia is regulated by the kidneys, which dispose of excess K+. Physiological central nervous system (CNS) K+ levels are involved in nerve signaling and hyperkalemia can dysregulate normal brain processes and it may also play a role in neuroinflammation. Increased K+ can cause muscle weakness, fatigue, and, in severe cases, even cognitive dysfunction with confusion, disorientation, and coma. An abnormality in K+ levels can be reflected in the membrane potential of neurons and affects their polarization and excitability. Mild hyperkalemia can cause increased neuronal excitability, muscle spasms, paresthesias, and neuronal and muscular paralysis with respiratory failure and/or cardiac arrhythmias.

KEYWORDS: *Hyperkalemia, potassium, brain, neuron, membrane potential*

INTRODUCTION

Hyperkalemia is a pathology that varies from mild to severe and very often also involves neuronal dysfunction. Hyperkalemia is a common electrolyte abnormality with high levels of potassium (K+) in the blood (1). It can significantly impact brain function and may cause neuroinflammation (2). Hyperkalemia can result in life-threatening arrhythmias and is associated with an increased risk of mortality (3). The development of hyperkalemia is often exacerbated by concomitant comorbidities such as diabetes mellitus or cardiovascular diseases (4). Hyperkalemia is managed by eliminating risk factors and through interventions aimed at directly lowering serum K+.

Most intracellular K+ is contained in muscle cells where it acts on the membrane potential. The physiological effect of this electrolyte depends on a normal serum concentration. K+ concentration decreases after renal excretion and sequestration of muscle and liver cells (5). K+ remains stable between meals due to its release mainly from muscle and liver cells. The distribution of K+ between the intracellular and extracellular space is maintained by balancing the activity of the Na/K-ATPase with K+ leak (6) (Table I). Effectors of K+ uptake and leak include insulin, catecholamines, mineral corticoids, tonicity, exercise, and acid-base status (7). More than 95% of K+ resides intracellularly and most of it is absorbed in the small intestine.

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Table I. *Na^+/K^+ ATPase dysfunction can cause the following dysfunctions to occur.*

- Accumulation of intracellular Na^+ and accumulation of extracellular K^+.
- Alteration of channels affecting repolarization.
- The elevation of K^+ normally stimulates aldosterone release via the adrenal cortex by increasing expression of the Na^+/K^+ ATPase channel in the kidneys for K^+ excretion.
- Impaired aldosterone function (Addison's disease, ACE inhibitors) worsens hyperkalemia.

Increased K+ intake causes hyperkalemia which may result in impaired renal excretion and/or cellular redistribution (8). The kidney has an important role in maintaining K+ homeostasis and healthy kidneys possess a great ability to dispose of excess K+, maintaining normal K+ serum levels even with intakes as high as 400 mmol per day (9). Most of the filtered K+ is reabsorbed in the proximal convoluted tubule and the loop of Henle. Renal K+ balance is largely determined by K+ secretion occurring in the distal nephron and collecting duct (10).

DISCUSSION

In the brain, K+ is crucial for nerve signaling and for central nervous system (CNS) functioning, but excessive levels can disrupt normal neurological processes (11). Hyperkalemia is defined as an elevated level of K+ in the blood. It can significantly impact brain function and may contribute to neuroinflammation (12). In the brain, K+ is crucial for nerve signaling and CNS function, but excessive levels can disrupt normal neurological processes (13). Hyperkalemia impairs nerve transmission, causing muscle weakness, fatigue, and in some cases, even paralysis (14). In addition, severe cases of hyperkalemia can cause cognitive dysfunction with confusion, disorientation, and coma (12). In rarer cases, seizures can occur due to disrupted neuronal excitability.

K+ is also an important element for the function of immune cells (15). In cases of hyperkalemia, there may alterations in the functioning of immune cells, such as T lymphocytes, causing an Ig deficiency, because, in the immune system, antibody-producing B lymphocytes and T cells (particularly IL-4-producing T helper cells) are interdependent (16). Excess K+ can affect other immune cells such as macrophages by altering their ability to phagocytose infectious agents and to present antigen correctly (17,18). Immune dysfunction due to hyperkalemia affects inflammation and activation of the NLRP3 inflammasome (19). High extracellular K+ inhibits the NLRP3 inflammasome, reducing excessive inflammatory responses. In hyperkalemia, the dysregulation of immune cells can lead to chronic inflammatory disorders, while initially it may suppress inflammation (20).

Hyperkalemia significantly affects neurons because of the crucial role of K+ in maintaining resting membrane potential and neuronal excitability (21). Hyperkalemia causes neurons to depolarize from their resting membrane potential. Neurons maintain a resting membrane potential of about -70 mV, largely due to the Na^+/K^+ pump and K+ leak channels. Extracellular hyperkalemia reduces the K+ gradient with less influx, causing depolarization and mild hyperkalemia can produce increased neuronal excitability (22). If there is mild extracellular hyperkalemia of 5.5-6.5 mEq/L, neurons are more excitable because they are closer to the threshold for action potentials. These effects can lead to spontaneous or excessive discharges, potentially causing muscle spasms, paresthesias, or seizures, while severe hyperkalemia can lead to reduced excitability and paralysis. In severe hyperkalemia (>7.0 mEq/L), persistent depolarization inactivates voltage-gated Na^+ channels, preventing them from reopening for further action potentials. These effects cause neuronal and muscle paralysis, which may contribute to respiratory failure or cardiac arrhythmias (23).

Non-physiological neuromuscular transmission leads to muscle weakness and paralysis, clinical manifestations related to neuronal dysfunction (24). In addition, abnormal sensations such as tingling or numbness (paraesthesia), and in extreme cases, seizures, and altered mental states such as confusion, lethargy, or coma may occur (25).

CONCLUSIONS

Hyperkalemia disrupts neuronal function by altering the resting membrane potential and action potential generation. Mild cases increase excitability, while severe cases lead to neuronal paralysis. Proper management of K+ levels is essential to prevent life-threatening complications.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Cox M, Sterns RH, Singer I. The Defense against Hyperkalemia: The Roles of Insulin and Aldosterone. *New England Journal of Medicine*. 1978;299(10):525-532. doi:https://doi.org/10.1056/nejm197809072991007
2. Samuels M, Seifter J. Encephalopathies Caused by Electrolyte Disorders. *Seminars in Neurology*. 2011;31(02):135-138. doi:https://doi.org/10.1055/s-0031-1277983
3. Diercks DB, Shumaik GM, Harrigan RA, Brady WJ, Chan TC. Electrocardiographic manifestations: electrolyte abnormalities. *The Journal of Emergency Medicine*. 2004;27(2):153-160. doi:https://doi.org/10.1016/j.jemermed.2004.04.006
4. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *European Heart Journal*. 2021;43(6). doi:https://doi.org/10.1093/eurheartj/ehab777
5. Halperin ML, Kamel KS. Potassium. *The Lancet*. 1998;352(9122):135-140. doi:https://doi.org/10.1016/s0140-6736(98)85044-7
6. Mayan H, Farfel Z, Karlish SJD. Renal Mg handling, FXYD2 and the central role of the Na,K-ATPase. *Physiological Reports*. 2018;6(17):e13843. doi:https://doi.org/10.14814/phy2.13843
7. Thier SO. Potassium physiology. *The American Journal of Medicine*. 1986;80(4A):3-7. doi:https://doi.org/10.1016/0002-9343(86)90334-7
8. Shustin L, Wald H, Popovtzer M. Role of down-regulated CHIF mRNA in the pathophysiology of hyperkalemia of acute tubular necrosis. *American Journal of Kidney Diseases*. 1998;32(4):600-604. doi:https://doi.org/10.1016/s0272-6386(98)70023-x
9. Dussol B. Équilibre potassique, hypokaliémie et hyperkaliémie. *Néphrologie & Thérapeutique*. 2010;6(3):180-199. doi:https://doi.org/10.1016/j.nephro.2010.03.004
10. Edoardo Sciatti, D'Elia E, Balestrieri G, D'Isa S, Attilio Iacovoni, Senni M. In pursuit of balance: renin–angiotensin–aldosterone system inhibitors and hyperkalaemia treatment. *European Heart Journal Supplements*. 2023;25(Supplement_C):C301-C305. doi:https://doi.org/10.1093/eurheartjsupp/suad053
11. Schmid G, Chittolini R, Raiteri L, Bonanno G. Differential effects of zinc on native GABAA receptor function in rat hippocampus and cerebellum. *Neurochemistry International*. 1999;34(5):399-405. doi:https://doi.org/10.1016/s0197-0186(99)00043-1
12. Hamed SA. Neurologic conditions and disorders of uremic syndrome of chronic kidney disease: presentations, causes, and treatment strategies. *Expert Review of Clinical Pharmacology*. 2019;12(1):61-90. doi:https://doi.org/10.1080/17512433.2019.1555468
13. Raiteri L, Zappettini S, Milanese M, Fedele E, Raiteri M, Bonanno G. Mechanisms of glutamate release elicited in rat cerebrocortical nerve endings by "pathologically" elevated extraterminal K^+ concentrations. *Journal of Neurochemistry*. 2007;103(3):952-961. doi:https://doi.org/10.1111/j.1471-4159.2007.04784.x
14. Larsen LH, Z'Graggen WJ, Bostock H, Tan SV, Buus NH, Tankisi H. The role of potassium in muscle membrane dysfunction in end-stage renal disease. *Clinical neurophysiology*. 2021;132(12):3125-3135. doi:https://doi.org/10.1016/j.clinph.2021.09.012
15. Matuszkiewicz-Rowinska J, Malyszko J. Prevention and Treatment of Tumor Lysis Syndrome in the Era of Onco-Nephrology Progress. *Kidney and Blood Pressure Research*. 2020;45(5):645-660. doi:https://doi.org/10.1159/000509934
16. Sitprija V. Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. *Nature Clinical Practice Nephrology*. 2008;4(2):91-101. doi:https://doi.org/10.1038/ncpneph0695
17. Sethi R, Pravesh Vishwakarma, Pradhan A. Evidence for Aldosterone Antagonism in Heart Failure. *Cardiac failure review*. 2024;10. doi:https://doi.org/10.15420/cfr.2024.10
18. Yentis SM. Suxamethonium and hyperkalaemia. *Anaesthesia and Intensive Care*. 1990;18(1):92-101. doi:https://doi.org/10.1177/0310057X9001800114
19. Deng L, Shi C, Li R, et al. The mechanisms underlying Chinese medicines to treat inflammation in diabetic kidney disease. *Journal of Ethnopharmacology*. 2024;333:118424-118424. doi:https://doi.org/10.1016/j.jep.2024.118424

20. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management. *JAMA*. 2019;322(13):1294-1304. doi:https://doi.org/10.1001/jama.2019.14745
21. Z'Graggen WJ, Bostock H. Nerve membrane excitability testing. *European Journal of Anaesthesiology*. 2008;25:68-72. doi:https://doi.org/10.1017/s0265021508003505
22. Paterson DJ. Potassium and Breathing in Exercise. *Sports Medicine*. 1997;23(3):149-163. doi:https://doi.org/10.2165/00007256-199723030-00002
23. Kim MJ, Valerio C, Knobloch G. Potassium Disorders: Hypokalemia and Hyperkalemia. *PubMed*. 2023;107(1):59-70.
24. Fontaine B, Khurana T, Hoffman E, et al. Hyperkalemic periodic paralysis and the adult muscle sodium channel alpha-subunit gene. *Science*. 1990;250(4983):1000-1002. doi:https://doi.org/10.1126/science.2173143
25. Hayes S, Wiese C, Schneidewend R. Tumor Lysis Syndrome following a Single Dose of Nivolumab for Relapsed Small-Cell Lung Cancer. *Case Reports in Oncology*. 2021;14(3):1652-1659. doi:https://doi.org/10.1159/000519566