Ebola: Destroys Na\textsuperscript{+}/K\textsuperscript{+} Ion Exchange to Accelerate Electrolyte Imbalance by Scorpion Venom-like System

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Abstract

Ebola sickness is a hemorrhagic fever caused by the Ebola virus that has an extremely high fatality rate. Electrolyte imbalance is a typical sign in Ebola patients who have already contracted the virus. The use of bioinformatics calculation tools to research Ebola's electrolyte imbalance mechanism is critical for halting the development of the epidemic and saving lives. The computational method of conserved domain search was employed to investigate the protein function of EBOV in this work. This study demonstrates that L, N, S, VP24, and VP35 have LCN type CS-\(\alpha/\beta\) domains. It is a peptide neurotoxin found in scorpions, sea anemone, and snake venom. It can activate Na\textsuperscript{+} channels and gradually deactivate them, and deactivate voltage- and Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels. S LCN type CS-\(\alpha/\beta\) is a neurotoxin with a lengthy chain that can activate Na\textsuperscript{+} channels. VP24, VP35, and N LCN type CS-\(\alpha/\beta\) are short-chain toxins that inhibit voltage-dependent or Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels and partially inactivate sodium channels. L contains both long- and short-chain LCN type CS-\(\alpha/\beta\) toxins that can activate Na\textsuperscript{+} channels and inhibit K\textsuperscript{+} channels. These LCN type CS-\(\alpha/\beta\) can activate Na\textsuperscript{+} channels and Na\textsuperscript{+}/K\textsuperscript{+} pumps while simultaneously inactivating K\textsuperscript{+} channels. It may result in many Na\textsuperscript{+} entering the cell and a large amount of K\textsuperscript{+} accumulating within the cell. Simultaneously, the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange pump outputs Na\textsuperscript{+} and inputs Ca\textsuperscript{2+} in “the reverse” mode. The results in an electrolytic environment outside the cell with hyponatremia, hypocalcemia and hypokalemia.

Keywords: LCN type CS-\(\alpha/\beta\): Hyponatremia; Hypocalcemia; Hyperkalemia; Hypokalemia;

1. Background

Ebola virus (EBOV) is the infectious agent that causes Ebola hemorrhagic fever (EVD). The ultimate hosts of EBOV are apes, humans, and other mammalian species vulnerable to infection (1). In 1976, Zaire (now the Democratic Republic of the Congo) had the first outbreak of Ebola virus disease(2). Since 1976, more than 25 outbreaks of EVD have been documented in Africa, and five distinct EBOV species have been identified(3). The Zaire Ebola virus is the most lethal strain, with a 90% death rate(4). Between March 2014 and the end of January 2015, the West Africa outbreak claimed over 22,000 lives and resulted in over 8,800 cases(3). African countries continue to experience isolated epidemics on a modest scale. Clinical care of Ebola virus disease continues to be complicated. Routine laboratory examination is typically not practicable in an outbreak setting, and data on associated hematological and biochemical abnormalities are scarce(5). Patients with EVD have been treated with specialized antiviral medication(6). There is
no effective treatment for EVD other than supportive care (7). Thus, understanding the Ebola virus's pathogenic mechanism is critical for halting the development of the epidemic and saving lives.

EBOV is a virus with an encapsulated filamentous RNA genome that is a member of the filovirus family. EBOV encodes seven structural proteins and two non-structural proteins (8): the 3'non-coding region (leader), the nucleoprotein (NP), VP35, VP40, three glycoproteins (sGP/ssGP/GP1,2), VP30, VP24, and the RNA-dependent RNA polymerase protein (L-polymerase). The virus is transmitted via mucosal membranes, wounds, and abrasions that come into contact with infectious material (blood, sweat, urine, and other secretions). Consumption of contaminated food containing high virus titers may also contribute (9). EBOV may infect many cell types, with a preference for rapid replication in monocytes, macrophages, and dendritic cells. The infection spreads via the lymphatic and circulatory systems (10). A significant proportion of lymphocytes suffer apoptosis and release soluble factors (11), initiating an inflammatory cascade and causing endothelium damage (12). Extensive necrosis of adrenal cortex cells occurs due to EBOV replication and prolonged infection. It impairs steroid synthesis, blood pressure regulation, and salt loss, resulting in hypovolemic shock (13). Diffuse intravascular coagulopathy and hypotensive shock are potentially fatal complications.

Positive IgM antibodies or an elevated IgG titer are strong indicators of a recent Ebola virus infection (14). Symptoms manifest between two and twenty-one days (most typically eight to ten days) following exposure to the Ebola virus. Fever, headache, joint and muscle aches, weakness, diarrhea, vomiting, stomach pain, loss of appetite, and abnormal bleeding are all signs of EBOV (14). The 2014 West Africa epidemic's most prevalent symptoms included fever, tiredness, vomiting, diarrhea, and anorexia (15). Diarrhea, vomiting, stomach pain, and dehydration are all common symptoms (16). Vomiting and diarrhea, and severe kidney injury can result in hypovolemic shock (17). When patients have collapse, neurological manifestations, and bleeding signs, they are in danger of deteriorating (18). Conjunctival congestion, epistaxis, bleeding gums, hemoptysis, purpuric rash, hematuria, fluid jet from injection or venipuncture sites, or other indicators of bleeding are all examples of bleeding symptoms. Severe individuals exhibit gradual declines in platelet counts, and hemoglobin levels (17). Diffuse intravascular coagulation, elevated creatinine, a large anion gap, and anemia are prevalent. Renal failure, hypocalcemia, and anemia all independently raise the risk of death (19). Ebola patients have a very high fatality rate. According to the virus strain, the case fatality rate (CFR) for all patients is 72 percent (3). In contrast, the case fatality rate (CFR) for hospitalized patients is slightly lower (60 percent) (3).

In West Africa, the case fatality rate is at least 70%. Those with respiratory, neurological, or bleeding symptoms are at an increased mortality risk (15). Increased urea and creatinine levels in the blood are markers of severe dehydration and compromised renal function and are strongly associated with mortality. Typically, Ebola disease is associated with potentially fatal electrolyte abnormalities and organ failure (20). Dehydration and electrolyte imbalances are significant causes of death (21). Low serum potassium, sodium, and calcium values are prevalent in Ebola patients (22). A substantial fluid loss from the gastrointestinal system results in insufficient volume, metabolic problems (including hyponatremia, hypokalemia, and hypocalcemia), shock, and organ failure (15). Hyponatremia is defined as a serum sodium content of less than 135 mmol/L, which is a condition that frequently occurs in Ebola virus sickness. Hyponatremia can result in brain edema and increased intracranial pressure, with symptoms such as headache, confusion, lethargy, seizures,
and coma(23). While hyponatremia is common in Ebola patients, excessive sodium syndrome is uncommon(19). To achieve optimal treatment, it is necessary to adjust for fluid and electrolyte loss carefully(15). Sodium chloride injections can be used to treat hyponatremia(23).

Sodium regulatory disorders are frequently related to defective sodium ion channel function. Specific viral regulatory proteins appear to be related to cell membrane fusion proteins(24). In general, viral proteins activate the Na+ channel, allowing Na+ to infiltrate the cell(25). The cell's Na+/Ca2+ exchange pump subsequently discharges some Na+ and absorbs Ca2+(25). S1 and S2 of the SARS-COV-2 S protein contain LCN type CS-a/β domain. LCN type CS-a/β denotes the cysteine-stabilized -helix/-sheet. The LCN type CS-a/β interacts to the extracellular -scorpion and amonene toxin receptors of the Na+ channel(26). It activates the Na+ channel, then a large number of sodium ions into the cell. Na+/K+ ATPase pumps 3 Na+ out of the cell and 2 K+ into the cell (active transport)(27). Na+/K+ ATPase is required for the proper functioning of numerous cell activities. When the K+ concentration inside the cell is greater than the K+ concentration of outer, K+ can release from the cell via the potassium ion channel (diffusion transport)(28). The majority of short-chain toxins LCN type CS-a/β are capable of inhibiting voltage-dependent or Ca2+-activated K+ channels(29). So LCN type CS-a/β can activate Na+/K+ pumps and Na+ channels while simultaneously inactivating K+ channels. It may result in many Na+ entering the cell(30, 31) and a large amount of K+ accumulating within the cell. Simultaneously, the Na+/Ca2+ exchange pump outputs Na+ and inputs Ca+ in “the reverse” mode(32). Na+ can also enter the cell via the Na+ channels. The results in an electrolytic environment outside the cell with hyponatremia, hypocalcemia and hypokalemia. A neurotoxic of the LCN type CS-a/β domain is found in scorpion venom, sea anemone venom, and snake venom.

The significant cations in human plasma are Na, K, Ca, and Mg, which are critical for maintaining the extracellular fluid's osmotic pressure, fluid distribution, and fluid transfer; the significant anions in extracellular fluid are Cl- and HCO3-. Along with maintaining the tension of bodily fluids, the two contribute significantly to acid-base balance. In normal circumstances, the total amount of anions in bodily fluid equals the total number of cations, and the fluid remains electrically neutral. When the concentration of any electrolyte changes, it results in various types of physiological harm, referred to as electrolyte imbalance. Venom from scorpions is naturally poisonous. Systemic symptoms associated with severe scorpion stings include dizziness, drowsiness, weakness, drooping eyelids, vomiting, diarrhea, abdominal pain, rigid mouth and tongue muscles, muscle cramps, foaming at the mouth, difficulty swallowing, slowed breathing, decreased blood pressure, and even coma. Ebola disease symptoms, which include vomiting, diarrhea, muscle pain, and bleeding, are strikingly similar to scorpion (snake) poisoning. It shows that the Ebola virus protein also has LCN type CS-a/β domains.

Na+ and K+ are both involved in the infection and proliferation of EBOV. Following receptor interaction between GP1 and the host TIM-1 receptor, EBOV is internalized mostly via the macropinocytosis pathway into the endosome. After EBOV is endocytosed, the GP1 domain is cleaved in the acidic endosome by the cell cathepsin. Then the Niemann-Pick C1 (NPC1) receptor binding site was revealed. Acidic pH and Ca2+ ions alter GP2s conformational equilibrium, conducive to the NPC1 combination's intermediate state(33). Amiloride, a Na+/K+ exchanger, has been shown to limit the various viruses that enter host cells via the macropinocytosis route(34). Amiloride also effectively prevents EBOV entrance and infection at non-cytotoxic levels in a dose-dependent manner(34). Digoxin and digitoxin are also frequently utilized as Na+/K+-ATPase
pump inhibitors in clinical practice. The active transport mechanism of adenosine triphosphate (Na+/K+-ATPase) is activated by sodium and potassium ions with particular antibodies(35). Anti-big-chain antibodies identify antigenic sites on large subunits exclusively on the inner surface of the plasma membrane of intact cells(35). When ferritin-coupled gamma-globulins bind to Na+/K+-ATPase at a saturated concentration, they do not inhibit the enzyme(35). Ebola virus VP24 is required for viral germination and export(36). During Ebola virus (EBOV) replication, a tight connection between ATP1A1 of the Na+/K+-ATPase and VP24 was discovered(34). Disrupting the action of ATP1A1 in Ebola virus-infected cells using small molecule inhibitors results in a decrease in offspring viruses(37). At a non-cytotoxic dose of 20 nM, the Na+/K+-ATPase pump inhibitor ouabain inhibits EBOV replication in human MRC-5 cells(38).

Potassium is required for the enveloped RNA virus spikes protein to undergo conformational modifications when fusion(39). Dengue virus capsid protein binding to liver lipid droplets (LD) is potassium ion-dependent and is mediated by LD surface proteins(40). Dengue fever virus (DENV) capsid protein (C) interacts with very-low-density lipoprotein (VLDL), exploiting the cell's high potassium content(41). It is not with low-density lipoprotein (LDL). This contact is potassium-dependent and involves the DENV C N-terminal region, similar to the DENV C-lipid droplet (LDs) interaction previously discovered(41). The production of DENV lipid virus particles may be the ideal vehicle for releasing the new virus into the extracellular environment. The viruses are ultimately reaching the new target cell. Infection with the Bunya virus is also prevented by modulating potassium channels(42). Bunia virus infection via the envelope requires an increased potassium ion concentration [K+]. The mechanism of virus transport via mature endosomes is regulated by the cell's K+ channel(39). K+ channel blockers limit Hazara virus (HAZV) infection, suggesting the K+ channel as a potential anti-bunia mechanism. When type 1 immunodeficiency virus (HIV-1) infects CD4+ cells, the intracellular potassium (K+) concentration increases(43). A low K+ medium limits the production of HIV-1 proteins, whereas a high K+ medium promotes the synthesis of HIV-1 proteins(43). Before hemolysis of Newcastle disease virus (NDV) , potassium is rapidly released from the cell, increasing the cell's cation permeability, then cell swelling and lysis(44). Potassium may play a role in the Ebola virus protein's conformational structural alterations. The unusual tissue bleeding or spurring symptoms observed in Ebola patients. It may be due to cell enlargement and lysis produced by an osmotic pressure imbalance of the K+ cation.

Numerous Ebola patients have an electrolyte environment deficient in potassium and require potassium supplementation via oral and intravenous routes(43). Children with severe Ebola virus disease have hypokalemia, which can be treated with intravenous and oral potassium(45). Patients with Ebola continued to experience diarrhea throughout their stay, resulting in significant loss of bodily fluids, necessitating ongoing IV potassium chloride infusions(46). Severe hypokalemia manifests in EVD by overall lethargy and tiredness, muscle necrosis, reduced respiratory function, and dysrhythmia induced by upper paralysis(47). While hypokalemia is common in people with Ebola, severe hypokalemia and hyperkalemia are uncommon(19). It shows a portion of potassium may be excreted in bodily fluids such as diarrhea and urine. The Ebola virus may also utilize another portion of potassium. When the Ebola virus enters the cell, potassium enters the vesicle by the cell's endocytosis. When the endosome releases virus nucleic acid, the endosome's potassium is released into the cytoplasm via potassium ion channels, which participates in the virus replication process. In other words, when the body is infected on a broad scale, a large amount of
potassium is introduced into the cells. The results in an abnormally low potassium level in the blood. Beside, the Ebola virus proteins blocked potassium flow from the intracellular to the serum or body fluids along potassium gradient by the LCN type CS-α/β domain. Potassium is crucial in the virus's release process. The potassium may be release outside the cell to maintain the conformation of structural proteins such as S. When a large amount of virus is released into the blood or the body fluid, extraordinarily high blood potassium levels are likely to occur.

The domain search method was employed to investigate the protein function of EBOV in this work. The results indicate that L, N, S, VP24, and VP35 have LCN type CS-α/β domains. S LCN type CS-α/β is a neurotoxin with a lengthy chain that can activate Na⁺ channels. S protein is involved in virus entry into the cell. It can activate the Na⁺ channel and Na⁺/K⁺ pump in the extracellular area. Then it facilitates the injection of a significant amount of Na⁺ into the cell function. The LCN type CS-α/β domains of VP24, VP35, and N are short-chain toxins that can inhibit voltage-dependent or Ca²⁺-activated K⁺ channels, as well as partially activate sodium channels. Both VP24 and VP25 contribute to the regulation of viral genome replication and transcription(48), as well as viral budding(49). N and L proteins play a direct role in the replication and transcription of viral genomes. So, N, L, VP24, and VP35 can regulate the intracellular region of the K⁺ channel and Na⁺/K⁺ pump and thus inhibit K⁺ ion output.

2. Method

2.1 Data set

1. The sequences of Ebola proteins. The Zaire ebolavirus proteins’ sequences came from the Uniprot database. S(Spike), N (Nucleoprotein), L(RNA-directed RNA polymerase), VP24 (Membrane associated protein), VP35 (Polymerase cofactor), VP30 (Transcriptional activator), VP40(Matrix protein) and Second non-structural secreted glycoprotein were selected.

2. Related sequences. The 731 LCN type CS-α/β related sequence was downloaded from UniProt data set. Keywords is “LCN+CS-α/β”.

2.2 The localized MEME tool of scanning for conserved domains

The analysis steps are listed as follows (for example, S protein):

1. Downloaded MEME from the official website and subsequently install it in the virtual machine ubuntu operating system. The virtual machine was VM 15.2.

2. Downloaded the Ebola S protein sequence from NCBI official website.

3. Downloaded the fasta format sequence such as LCN type CS-α/β-related ones from Uniprot official website, respectively.

4. For each sequence in all LCN type CS-α/β-related protein, paired with each Ebola S protein sequence to generate fasta format files for MEME analysis.

5. For the files generated in Step 4, a batch of 50000 was used to create several batches, and it was considered as the limited space of the virtual ubuntu system.

6. In ubuntu, searched the conserved domains (E-value<=0.05) of Ebola S protein and LCN type CS-α/β-related with MEME tools in batches.

7. Collected the result files of conserved domains. Then, found the domain name corresponding to the motif from the uniprot database.

8. The domains’ activity of each Ebola S protein was analyzed according to the
3. Results

3.1 Ebola proteins have LCN type CS-α/β domains

LCN type CS-α/β domain (IPR044062) is a cysteine-stable / (CS-α/β) domain of the LCN type. Interpro database describes that the CS-α/β domain of the LCN type is composed of one or two short -helical segments, and two disulfide bonds are joined to make a triple-stranded -sheet. The variable area is connected to form a loop. Scorpion venoms contain neurotoxins (proteins with a low molecular weight), cardiotoxins, hemolytic toxins, antimicrobial peptides, enzymes (such as hyaluronidase, acetylcholinesterase, phospholipase, and metalloprotease), lipids, nucleotides, and mucopolysaccharides, as well as a complex mixture of biogenic amines.

Table 1. LCN type CS-α/β domains of Ebola proteins

| Protein | Alias | Motif | Start | End | Length | Cys |
|---------|--------|-------|-------|-----|--------|-----|
| L       | A      | FCPVEPRCQQFLDEIKYTMQDALFLKYLYLKNVGAQEDCVD | 89 | 154 | 66 | V   |
|         |        | DHFQEKILSSIQGNEFLHQMFYWYD |  |   |     |     |
|         | B      | CWDAVFEPNVLGYNPPHK | 493 | 510 | 18 | V   |
|         | C      | KYNVFYETAPFIEYCNRCYGVKNFNWMMHTIPQCYM | 635 | 710 | 76 | V   |
|         | D      | DEMVCKWL | 1013 | 1020 | 8 | V   |
|         | E      | PCMIEQFKVVLKPYEHCRCSCNAAKQPG | 1133 | 1161 | 29 | V   |
|         | F      | YCRFTGIVSSMHYKLDEVLEIE | 1803 | 1825 | 23 | V   |
|         | G      | VCNRFYHIRDNCEE | 2160 | 2174 | 15 | V   |
| N       | A      | VVMTPSLTESDMDYHKILTAGLSVQQGIVRQRVIPVYQ | 8 | 45 | 38 | V   |
|         | B      | FLLMLCLHHAYQGDYKLFLESGAVKYLE | 73 | 100 | 28 | V   |
|         | C      | FRFEVKKCDGV | 104 | 114 | 11 | V   |
|         | D      | GHDAND | 183 | 229 | 47 | V   |
|         | E      | YGEYQSYSENGMS | 466 | 478 | 13 | V   |
|         | F      | TGPRLTHHSAPLTDNRRPEGSSTPRMLTPIN | 531 | 566 | 36 | V   |
|         | G      | GKEYTYPDS | 642 | 691 | 50 | V   |
|         | H      | YPPWLTEKEAMNDFRNFRVTLDGQFQYWPVMNHKNRFMAILQHH | 696 | 738 | 43 | V   |
| S       | A      | EWAENCYNL | 103 | 111 | 9 | V   |
|         | B      | WGTHCLGPDCIEPHDWTKNITKIDQIHHDFDKLTDQ | 597 | 654 | 58 | V   |
|         |        | GDNDDNWGTGWQWPAPA |       |     |     |     |
| VP24    | A      | CNFLVSQTIQGWKVYYWAGIEFDVTGHGMA | 27 | 55 | 29 | V   |
|         | B      | NHFNRTQ | 132 | 139 | 8 | V   |
| VP30    | A      | KGSFEALWQQDWRQLSMIFITAFLNI | 218 | 245 | 28 | V   |
| VP35    | A      | YDMAKTISSLNRVCAEMVAKY | 122 | 142 | 21 | V   |
|         | B      | ENFGKPDIAKDLRNMIDHLPFGTAFHVQLVQVICKLGKS | 212 | 253 | 42 | V   |
| VP40    | A      | EYMEAIY | 12 | 18 | 7 | V   |
|         | B      | IGNNQAFQEFVLPPVQLPQYFT | 152 | 174 | 23 | V   |
The LCN-type CS-α/β domain is a neurotoxin found in scorpion venom classified as either short-chain or long-chain. They share a structural motif known as the cysteine-stabilized-helix/sheet motif (CS-α/β). Short LCNs are typically composed of 30-40 residues and three or four disulfide linkages. The majority of short-chain toxins inhibit voltage-dependent or calcium-dependent K⁺ channels. Most long-chain neurotoxins (LCN) include between 60 and 70 residues and are connected by four disulfide links. Long-chain or voltage-gated sodium channel scorpion neurotoxins (NaScTxs) are categorised as alpha toxins (delay the inactivation of Na⁺ channels) or beta toxins (inhibit the inactivation of Na⁺ channels) (influencing the process of channel activation). Both kinds inhibit inactivation of sodium channels.

From the UniProt database, we retrieved the Ebola proteins and LCN type CS-α/β related proteins. Then, using the local MEME tool, match the Ebola proteins to LCN type CS-α/β related proteins to look for conserved domains. Finally, the motif fragments were combined using the Ebola proteins and domains as a guide. The motifs of the search were indicated in Table 1.

As illustrated in Table 1, L, N, S, VP24, VP30, VP35, and VP40 all include LCN type CS-α/β domain segments. However, because the motif sequences of the LCN type CS-α/β domains of VP40 and VP30 did not contain Cys, the activity is ruled out. VP24 LCN type CS-α/β A, VP35 LCN type CS-α/β A-B, and N LCN type CS-α/β B-C all include Cys, indicating that their polymers may form disulfide bonds. Their length ranges between 30 and 40 nt. As a result, the LCN type CS-α/β domains of VP24, VP35, and N are short-chain toxins capable of inhibiting voltage-dependent or Ca²⁺-activated K⁺ channels. Additionally, it may result in an inadequate deactivation of sodium channels.

All S LCN type CS-α/β A-B contain Cys, indicating that they may form disulfide bonds. S LCN type CS-α/β B is close to 60 nt in length. LCN type CS-α/β A with a length of less than 30 nt may aid S LCN type CS-α/β B. As a result, S LCN type CS-α/β is a long-chain neurotoxic capable of activating Na⁺ channels.

Both L LCN type CS-α/β A-G include Cys, indicating that their polymers have the potential to form disulfide bonds. L LCN type CS-α/β A and C are both greater than 60 nt in length. It demonstrates that S LCN type CS-α/β A and C are long-chain neurotoxins capable of activating Na⁺ channels. L LCN type CS-α/β B, D-G is less than 30nt in length. They are short-chain toxins that inhibit voltage-dependent or Ca²⁺-activated K⁺ channels and also partially activate sodium channels.

3.2 Mechanism of Ebola proteins disrupting Na⁺/K⁺ ion exchange

Numerous Spike proteins were present on the virus surface. S LCN type CS-α/β was discovered to be capable of activating Na⁺ channels. Then a substantial amount of sodium ions were injected into cells. The surface of the Ebola virus made numerous contact sites with the cell membrane, increasing the number of Na⁺ channels activated by the S protein. Under these circumstances, a significant amount of sodium from the blood was entered into the cells through Na⁺ channels. Simultaneously, a significant amount of sodium was pumped out of the cell by Na⁺/Ca²⁺ pumps. A considerable amount of calcium was injected into the cell via the pumps. The Na⁺/K⁺ pump also pumped a large amount of sodium from the cell. It also injected a massive amount of potassium into the cell. Through the active Na⁺ channel, the pumped sodium out of the cell could also be reintroduced into the cell.

Unlike the SARS-COV-2 virus, the Ebola virus has an extremely high need for potassium during reproduction and dissemination. This present study discovered that LCN type CS-α/β of L,
N, VP24, and VP35 can interfere with K+ channels. It prevented intracellular K+ from being recycled into the blood and bodily fluids via the K+ channel. Eventually, a cell would develop an environment with elevated sodium, calcium, and potassium levels. Ebola patients' blood sodium, calcium, and potassium levels were lower than usual, resulting in hyponatremia, hypocalcemia, and hypokalemia.

4. Discussion

This present study discovered that the Ebola virus proteins contain an LCN type CS-α/β neurotoxic peptide. These peptides have the ability to open sodium channels and close potassium channels. These peptided act directly on Na+, K+ channels, and Na+/K+ pumps. The Na+/Ca+ pump will be indirectly regulated. The membranes of the majority of cells include these two pumps and two channels. It is critical for the stability of the cell structure and signal transduction. Suppose these two channels or pumps are not functioning correctly. In that case, aberrant functions in blood cells, immune cells, neuron cells, kidney cells, intestine cells, liver cells, and heart cells will occur.

Hyponatremia is a condition in which the plasma sodium concentration is less than 130mmol/L. Hyponatremia is manifested by insufficient intake (rarely), excessive loss, and an absolute or relative increase in water. It can be classified into two broad categories of factors: renal and non-renal. Hyponatremia due to renal impairment can occur due to osmotic diuresis, decreased adrenal function, or acute or chronic renal failure. Non-renal factors such as vomiting, diarrhea, intestinal fistula, excessive perspiration, burns, and other disorders all affect the disease process. The LCN type CS-α/β neurotoxic peptides of the Ebola virus proteins controled the Na+ channels in kidney and gastrointestinal cells, and then resulted in hyponatremia.

Hypokalemia is defined as a serum potassium level less than 3.5mmol/L. Hypokalemia can be caused by insufficient potassium intake or by the entrance of extracellular potassium into cells. Appetite loss, abdominal distension, thirst, nausea, vomiting, chest pain, and palpitations, as well as significant myocardial involvement, might result in heart failure, weaker limbs, weakness, flaccid paralysis, and periodic paralysis. In difficult situations, there may be confusion, lethargy, delirium, or coma. Hyperkalemia occurs when the serum potassium level exceeds 5.5mmol/L. Hyperkalemia can occur as a result of excessive potassium intake or potassium excretion issues. The LCN type CS-α/β neurotoxic peptide of the Ebola virus protein controled K+ channels of heart cells, kidney and gastrointestinal cells, and nerve cells. Hypokalemia-related physical, muscular, and mental symptoms may also develop.

Hypocalcemia is associated with various neuropsychiatric symptoms, including twitching of the hands and feet, epileptic seizures, paresthesias, increased muscle tone, tendon hyperreflexia, muscle tenderness, and altered state of consciousness, as well as bronchospasm, laryngospasm, and respiratory failure. Hypocalcemia is induced by hyponatremia, according to this present study. When intracellular sodium levels are elevated, infected cells inhale a significant amount of calcium via the Na+/Ca+ pump exchange route, resulting in a reduction in blood calcium. Calcium is a critical signaling molecule in neuron, immunological, and muscle cells. Inadequate Ca2+ levels in the bloodstream can result in neurological, immunological, and motor systems problems.

In summary, the Ebola virus protein hijacks Na+, K+ channels, and Na+/K+ pumps via the LCN type CS-α/β neurotoxic peptide, resulting in an unusually active Na+/Ca2+ pump.
5. Conclusion

Ebola disease is a hemorrhagic fever caused by the Ebola virus that has a 90% death rate. The 2014 West Africa outbreak was characterized by fever, tiredness, vomiting, diarrhea, and anorexia; acute electrolyte imbalance was a deadly factor. Clinical research on Ebola virus disease remains challenging, and statistical analysis of hematological and biochemical anomalies is limited. The electrolyte imbalance mechanism underlying Ebola sickness is critical for halting the epidemic’s progress and saving lives.

The domain search method was employed to investigate the protein function of EBOV in this work. The results indicate that L, N, S, VP24, and VP35 have LCN type CS-α/β domains. S LCN type CS-α/β is a neurotoxin with a lengthy chain that can activate Na+ channels. VP24, VP35, and N LCN type CS-α/β are short-chain toxins that inhibit voltage-dependent or Ca2+-activated K+ channels and partially activate sodium channels. This present study demonstrates that by utilizing an LCN type CS-α/β domain, S protein can activate Na+ channels and Na+/K+ pumps in extracellular areas, promoting a high rate of Na+ injection into the cell. N, L, VP24, and VP35 can regulate intracellular K+ channels and Na+/K+ pumps via LCN type CS-α/β domains, inhibiting K+ ion output. In Ebola patients, abnormal Na+ channel and Na+/K+ pump activity can result in hyponatremia; abnormal Na-Ca pumps can result in hypocalcemia; and abnormal K+ channel inactivation might result in severe hypokalemia symptoms.

Declarations

Ethics approval and consent to participation

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets and results supporting the conclusions of this article are available at: https://pan.baidu.com/s/1qfg0x5UK-4RW6r0C2SnqCQ; code: utoa
Or:https://mega.nz/folder/9u5XiQTL#0koikv9vO_KWJ5xSHStIlg

Competing interests

The authors declare that they have no competing interests.

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