ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 7 | July - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

SODIUM POTASSIUM ATPASE, ITS ROLE IN THE PATHOGENESIS AND TREATMENT OF INFECTIONS LIKE COVID-19 AND DENGUE, A REVIEW

Biochemistry

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ABSTRACT

In the region of West Bengal, a state of India the diseases like Dengue and Chikungunya are manifested in various part in this season with addition to a disease called Covid-19 related severe Acute Respiratory Syndrome (SARS) which become pandemic since its inception in February 20.So to develop a combating strategy and to find out their effects on human body we review a lot of literature. We found that it is Sodium Potassium ATPase which could play a very important role in the pathogenesis and treatment of said diseases. Sodium Potassium ATPase is a ubiquitous enzyme doing a bagful of cellular actions with its specific sub units. It was seen that these infections can lead to diminished even disruptions of function of this molecule leading to wide spread manifestations of diseases. Again a lot of drugs have been engineered to inhibit its specific sub unit so that partial inhibition of specific part can prevent the inception of these infections as well the potential treatment of infections once established. Already a lot of drugs particularly cardiac glycosides show a lot of promises. Our review article thus throws the light and conveys the message that the said enzyme and potential drug candidates are to be studied more thoroughly to overcome the scenario created by the diseases.

KEYWORDS

Sodium Potassium ATPase, Covid-19, Chikungunya , Cardiac Glycosides

INTRODUCTION

Sodium Potassium ATPase was discovered a long time ago around 1960[1].Its structure, function and every aspects of its physiology was thoroughly studied. It is a ubiquitous enzyme doing a bagful of specialized works starting from maintaining homeostasis of Ions in intracellular and extracellular environment by pumping out 3 Sodium out of the cell and giving entry to 2 Potassium ions to maintain membrane potential and acting as an important molecule for signaling pathway in protein kinase C (PKC) and phosphoinositide 3-kinase (PI3K) activation. [2–5]

Now we are shifting our focus towards the deadliest infection of the era, Corona virus or Covid-19 infection and its molecular mechanism to describe pathogenesis.Covid-19 is a single strand RNA virus mainly responsible for Severe Acute Respiratory Syndrome in populations residing in different geographical areas creating a pandemic situation overall. This virus particle is taking entry into human body by binding with Angiotensin Converting Enzyme II receptor or ACEII receptor of alveolar cells present in lungs. After its binding with the receptor it is endocytosed in vesicle in the cell by furin mediated endocytosis. [6] Now once entered intro cell it replicates and takes upper hand of cells transcription and translation machinery to channelize to form its own products which cause a widespread proinflammatory cytokine storm leading to multi organ failure or blocking numerous micro vessels with thrombi as a result from free radicle injury and inflammation. The inflammatory cascade can evolve a lot of events affecting many important biomolecules in our body. In different article and research papers researchers convinced that this widespread manifestations of this infection are due to affection of multiple organ and systems of the body [7,8-10].Though the causal association is yet to be ascertained a lot of theory regarding this issue has been proposed. After going through several article we found that the affection of Sodium Potassium ATPase can address the varied symptoms of this disease manifestation as well as pathogenicity and drug evolution. We now review how different RNA virus deal with Sodium Potassium ATPase in human body

The different manifestations seen in Sodium Potassium ATPase when infected by RNA viruses

The Sodium Potassium ATPase is down regulated by H1N1 and H5N1 infections in lung alveoli. The fluid clearance machinery and mechanism of lung are governed by the Sodium Potassium ATPase as well. So after binding and engulfment they affect the fluid clearance system of lung alveoli thus clogging the architectures of lung causing the respiratory distress. [11]

The membrane potential is deranged in the infections of coxsackie B in GI tracts and sindbis virus [12]resulting in both derangement of generation of action potential and also electrolyte imbalance in intracellular and extracellular environment.

On the contrary to this enterovirus 71(EV71) can increase Sodium potassium ATPase expression via interaction with β3 sub unit. [13].

RNA viruses are also affected by fine tuning of Sodium Potassium ATPase

We can describe a lot of events as seen in different RNA viruses when they are subjected to specific Sodium Potassium inhibitors. Ashbrook et al. in their journey to discover drugs effective against Chikungunya virus showed promising signs when they treated osteosarcoma cells by cardiac glycosides digoxin.Also promising and similar reults are seen against many other alpha viruses like sindbis virus,vesicular stomatitis virus,river virus etc mainly due to blockage of events of virus lifecycle after entry into cell typically via inhibition of Sodium Potassium ATPase.

Hoffmann et al opined after doing screening test of different drugs against dreaded drug resistant influenza infections that ouabain and lanatoside C were found effective in blocking viral replication after entry.

In a different study it was observed that at low doses of digoxin Corona viruses become susceptible probably via α1 subunit inhibition of Sodium Potassium ATPase. It was also found that an inhibitor of Src pathway can reverse the situation.

What are the possible barrier that can be formed by Sodium Potassium ATPase inhibitors in respect to COVID-19 infections

Firstly because of α1 sub unit inhibition of Sodium Potassium ATPase the viral entry can be prevented because of down regulation of surface receptor in lungs alveolar type 2 cells.

Secondly the intracellular environments become hostile to virus as Potassium level decreases in cells because of the said inhibition.

Thirdly Src activator can also produce barrier by causing internal signal pathway stimulation to rescue the effects of virus influence on Sodium Potassium ATPases. [14]

The potential drug candidates in this scenario

In vitro analysis of Drugs starting from anti epileptics like Chlorpromazine,antihistaminics like Promethazine and Cardio logical drugs like Verapamil and Propranolol was done in recent past.

The dose dependent inhibition is seen with these drugs. Although proper mechanism of action has to be elucidated. [15]

The role of cardiac glycosides is discussed in view of anti-viral effect

on different rna virus infections.

The role of anti-oxidant were discussed in many literature having a regenerating effects of already injured Sodium Potassium ATPase enzyme in the environment of free radicle OVID-19 infections. [16]

Potential challenging road maps of safety assurance of Sodium Potassium ATPase

Sodium Potassium ATPase is a crucial central molecule to which a lot of molecular events are dependent .So to protect it from immediate insult by COVID-19 is the first priority to say the least.

Now a little bit detail study of Sodium Potassium ATPase. This is a ubiquitous enzyme present almost in All the tissues of the body and have a specialized structure composed of several sub units. Our focus is mainly on α sub unit as it has the catalytic activity to do several works as Described earlier. [17] Till now 3 sub units of α type has been discovered. In previous studies it was seen that the sub units of this said enzymes are typically controlled by phosphorylation done by PKA,PKG and PKC.Non receptor tyrosine kinase particularly Src is the chief molecule in this regard. Now already we have discussed what multipurpose roles can be played by Sodium Potassium ATPase. So derangement of the molecule can cause many a clinical manifestation typically seen with Covid-19 infections like ATP depletion, widespread irregular cell membrane potential generation, fatiguability,dyselectrolytemia etc. [18]

Now to combat this spectrum of diseases what to do: try to stimulate Sodium Potassium ATPase but that can cause up regulation of receptors in lungs for the attachment of Covid-19 or to inhibit Sodium Potassium ATPase but also that can jeopardies almost all the essential functions related with this molecule.

Now after reviewing a lot of research papers we come across to point out that if Sodium Potassium ATP ase can be inhibited with one targeted sub units keeping other sub units unchallenged the goal can be reached. Already such molecules like cardiac glycosides in the form of digoxin and specific inhibitors like ouabain have studied in great details to play the desired level of works so far. While we are thinking about Covid-19 infections but also Dengue and Chikungunya already entered into scenario with all lethal repertoire in hand. [19]

We have literally found the solution, the right answer of these problems in the form of specific inhibitors of Sodium Potassium ATPase which can simultaneously handle the situations generated by these infections. A lot of researches regarding more specific inhibitors with intrinsic Src stimulators are taken up, a lot of commonly used drugs like propranolol, promethazine etc are chemically treated with the enzymes and a lot of promising result is coming out of these studies. [20]

Conclusion drawn from above discussions

Sodium Potassium ATPase is the ubiquitous enzyme plays a very critical role in the pathway of Covid-19 and other RNA virus infections. If infected with any of these infections Sodium Potassium ATPase is affected rather assaulted and once it is affected many important cellular functions hampered like electrolyte imbalance, membrane potential generation, nerve impulse transmission and a lot of components maintaining cellular homeostasis.

On the other hand in various studies it was evident that a specific inhibitor like cardiac glycosides can prevent the infections like Dengue, Chikungunya,Covid-19 by various mechanisms by altering the cascades of events starting from Sodium Potassium ATPase. Activation of Src pathway and specific inhibition of a part or sub units of Sodium Potassium ATPase can prevent and terminate these dreaded diseases simultaneously. So in this present scenario in our part of world where Covid-19 still causing a huge loss of life and again Dengue and Chikungunya are emerging from hibernation the activity of this wonderful molecule like Sodium Potassium ATPase to be judged with both pathogenesis point of view and development of combating strategies point of view.

Conflict of interest : NIL

Acknowledgement : All my faculty members ,my juniors and all post graduate trainees of the department of Biochemistry ,Medical college Kolkata.

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