Journal of Integrated
SCIENCE & TECHNOLOGY

Mathematical modeling of Ryanodine receptor for Alzheimer's disease

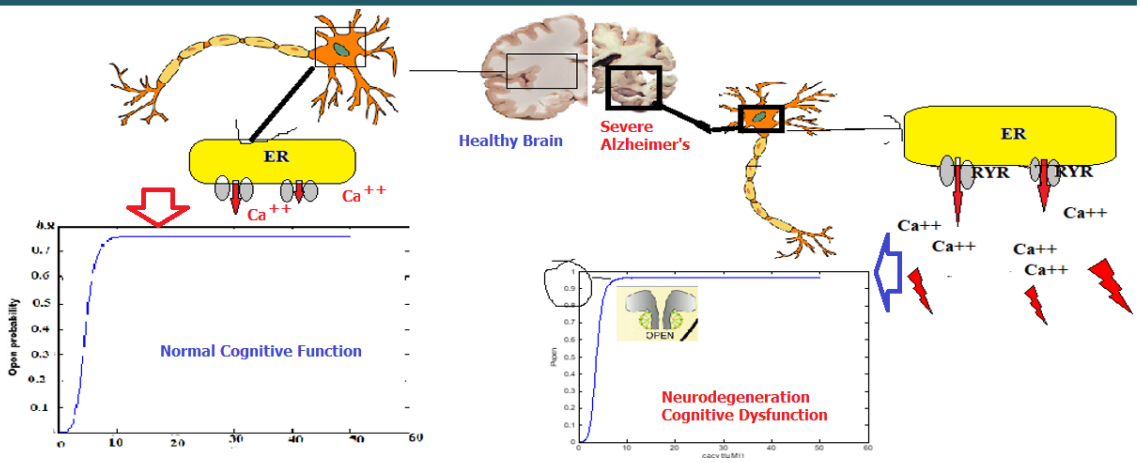
Sonupriya Roy,[1*] Vijay Dave,[2*]

[1]*Department of Biomedical Engineeirng, Institute of Technology, Ganpat University, Kherava, Gujarat, India.* [2]*Department of Biomedical Engineering, Government Engineering College. Sector-28, Gandhinagar, Gujarat, India*

Received on: 30-June-2023, Accepted and Published on: 07-Sept-2023

Article

ABSTRACT



Increased intracellular calcium is important for action potential, Long Term Potentiation (LTP) and Long-Term Depression (LTD), neuron transmitter release and many more. Calcium influx from channel, present on plasma membrane, is amplified by calcium release from Endoplasmic reticulum (ER) via IP3 and Ryanodine Receptor (Ryr). As there is increase in Ryr open probability and its expression in Alzheimer 's Disease (AD), so we targeted Ryr for further study. We studied the effect of AD on Ryr open probability, by varying the required parameter and compared it with open probability of Ryr in normal condition. We found a significant difference between open probability and calcium release response from Ryr. So, Ryr can be targeted for further therapeutic study, to control Ryr open probability using computational modelling.

Keywords: Alzheimer's disease, neurodegenerative disease, calcium, Ryanodine receptor, Open Probability

INTRODUCTION

Alzheimer's Disease (AD) which is progressive neurodegenerative disease cause cognitive, behaviour and memory impairment led to dementia most commonly in aged people, and there is no treatment for it so far.[1,2] About 30 million people suffered from Alzheimer, by estimated value, we can say that 5.7 million people in the U.S. have AD of whom 5.5 million are aged 65 years or older,[3] as there is increase in population of aged people (above 65), it is estimated that number going to be doubled by 2050.[4] In 2015-20 AD prevalent estimated at 760 per 100,000 inhabitant.[5] Generally, the presence of AD is described by presence of extracellular beta amyloid and intracellular neurofibrillary tangles(NFT). Tau which is highly phosphorylated, its phosphorylation decreases with aging and it binds with microtubule and makes it more stable. However, in AD, hyperphosphorylated tau forms clumps, results in blockage of nutrient transportation, and led to NFT, ultimately led to death of neurons.[6] The beta amyloid interfere with synaptic communication. It led to cognitive decline, memory loss.[3,7,8]

AD starts from Hippocampus, which is located in temporal lobe, is crucial part of limbic system and further divided into part of Cornu Ammonis.[9] Hippocampus, which is S shaped, is related to memory formation, here AD starts with neurodegeneration (damage to cortical neuron) results in shrinkage of hippocampus and is most severely affected.[9–11] Then it starts proliferate to other regions like temporal lobe, affecting limbic system, then to frontal lobe. There is reduction in neuron density, cornu ammonis (CA neurons), and highly in CA1 region, CA1 neuron contain pyramidal neuron (neuron which can be find in hippocampus) got damaged in AD.[12]

*Corresponding Author: Sonupriya Roy, Biomedical Engineering Department, Institute of Technology, Ganpat University,Kherava, India. Vijay Dave, Biomedical Engineering Department, Government Engineering College, Gandhinagar, India
Email: sonupriyaroy@gmail.com, vijaydave12@gmail.com

Cite as: *J. Integr. Sci. Technol., 2024, 12(1), 716. URN:NBN:sciencein.jist.2024.v12.716*

 ISSN: 2321-4635
http://pubs.thesciencein.org/jist

In neuron, Calcium is second messenger ubiquitous in nature, and is fundamental in cellular function. Calcium is maintained at required level in resting state, and its level increased during memory formation, which is vital for action potential, neurotransmitter release, Long term potentiation (LTP) and calcium is maintained at required concentration.[4,13] As, we discussed in review on modelling aspect of Ryanodine receptor(Ryr) for CA1 neuron that perturbance in calcium level, that is increase in calcium concentration beyond required level led to neurodegenerative disease AD, and this changes takes place prior to cognitive decline. In addition this led to NFT and shrinkage of hippocampus takes place.[14–16]

In Figure 1, Inside neuron calcium can be released from VGCC, RYR(can be found on Endoplasmic reticulum(ER)) and IP3(on ER) .As discussed in our previous work,[14] that in response of neurotransmitter release from presynaptic axon terminal, voltage gated calcium channel (VGCC) present at postsynaptic dendrites got activated and cause the influx of calcium., then the calcium which enters the intracellular level through VGCC interact with Ryr and caused it open and calcium release takes place at intracellular level, one of the intracellular calcium release channel Ryr and other is IP3(Ionsitol triphosohate), present on Endoplasmic reticulum(ER). In IP3, external stimuli acts on G-Protein, acts on phospholipase C and generate IP3, which diffuse from plasma membrane to ER, binds to ligand gated IP3 receptor, and cause it to open and efflux of calcium takes place into the cytosol. Hence, at intracellular level two calcium release channel is present on ER and that calcium release from IP3(Ionsitol Triphosphate) and Ryr is essential for various cellular function. Raised intracellular calcium is necessary for LTP, action hyperpolarization, cell survival and any many more. However, when it increased beyond required level that is in AD, it led to neuron cell death. In addition, increased calcium level results in increased activity of calpain, which led to formation of NFT. So all that contribute towards neuron loss. In normal cell, increased calcium takes up by mitochondria uniporter (MCU) and Sodium /Calcium exchange (NCX) moves the calcium out of cell. In molecular mechanism underlying SOCC (store operated calcium channel), protein used to sense the filling state of ER calcium is STIM (STromal Interaction molecule), and it sits in the ER membrane. On depletion of ER calcium STIM forms clusters in the ER region, which is closer to plasma membrane. At the same time, another protein, ORAI(with three mammalian homologs, Orai1, Orai2, and Orai3)which are on plasma membrane, congregates, on interaction with STIM forms calcium channel that allows calcium to enter from extracellular medium into the cytosol.[17–19]

In addition, deficient calcium in ER is refilled by SERCA pump from cytosol. However, in AD, malfunctioning of these channel takes place, which is having effect on calcium haemostasis balance, as it is essential for neuronal survival and memory formation (synaptic plasticity). In that there is increase in VGCC sensitivity results in increased calcium influx. In addition, there is increase in expression and open probability of Ryr. In AD, Presenilin act as leak channel and it also alters the normal function of SERCA pump. In IP3 excessive stimulation of mGlur linked with IP3 production and increased in calcium efflux takes place. Here, NCX got inhibited. Then increased intracellular calcium cause excessive calcium uptake by mitochondria, results in its overload, produce cytochrome C and that led to neuron cell death (Apoptosis).[14]

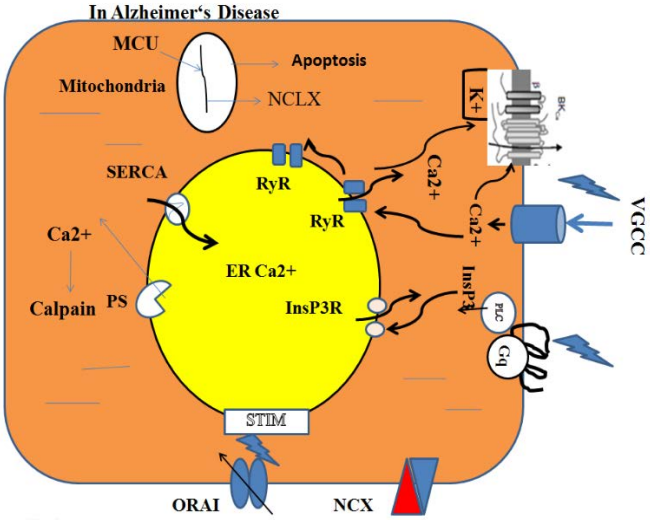


Figure 1. Calcium signalling in AD

Further, AD is related to memory formation disorder, experiment performed on Rodent model demonstrate that stimulation of Ryr improves memory formation, while its blockage results in amnesia. In addition, knockdown of Ryr having detrimental effect on memory formation that is LTP and LTD. In AD, there is increase in expression, open probability and flux of Ryr, results in increased calcium release in hippocampal region.[20] Dantrolene is known for inhibition of Ryr,[21,22] but it use increases overload of Ryr.[16,23] In addition, as we discussed desired intracellular calcium is required for normal function of cell. So it's required to reduce the open probability of Ryr by varying the required parameter. So, In AD, there is increase open probability of Ryr and flux through it, it is seen during earlier phase of AD, can be used for detection

Thus Ryr which is responsible for neuronal activity and due to its connection with AD, can be target for further study.[16]

Mathematical modelling is one of important model to understand the behaviour of channel. In this study, we simulate the open probability of Ryr. The aim of this simulation, is to study the effect of AD on open probability of Ryr by varying the required parameter and then it compared with the open probability of Ryr in normal condition.

METHODOLOGY

Computational modelling approach is a technique to study calcium signalling through simulations. It can be used to investigate the relation between intracellular channel and calcium. In calcium signalling model of ER, modelling is done for gating mechanism of channel. Ryr receptor are sensitive to intracellular calcium concentration. It activated (opening of receptor and release of calcium takes place) on the rise of intracellular calcium from nm to micro molar, whereas at higher micro molar levels of intracellular calcium, Ryr is inactivated.[22]

Open Probability is opening of channel and gradient that pass through it, is flux.

2.1 **Open Probability**

Keizer and Levine open probability model having gating kinetics, in this model, channel remains in two closed state, that is C1 and C2 and two open state O1 and O2.

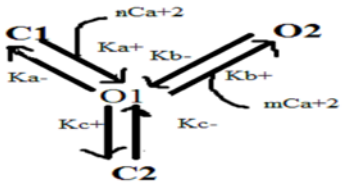


Figure 2. Schematic for transition in closed and open state.

In figure 2, schematic shows transition from C1 to O1 on binding of (m=4) calcium and from O1 to O2 on n=3 calcium, it corresponds to calcium induce calcium release (CICR). In addition, sum of four states that is two closed and two open states is C1+C2+O1+O2=1,when channel open the gradient flow from endoplasmic reticulum to cytoplasm. At Calcium 0.1 µM, most of channel are in state C1. Open probability of Ryr depends on cytosolic calcium concentration level and for Keizer and Levine model it varies from 0.1µM to 0.9 µM. The open probability Popen, can be expressed by:[14,24,25]

$$\text{Popen} = W((1+\left(\frac{\text{Cacyt}}{\text{Kb}}\right)^3)/((1+\left(\frac{\text{Ka}}{\text{Cacyt}}\right)^4+\left(\frac{\text{Cacyt}}{\text{Kb}}\right)^3) \quad \ldots(1)$$

$$W^{\infty}[\text{Cacyt}] = \frac{1+\left(\frac{\text{Ka}}{\text{Cacyt}}\right)^4+\left(\frac{\text{Cacyt}}{\text{Kb}}\right)^3}{1+\left(\frac{1}{\text{Kc}}\right)+\left(\frac{\text{Ka}}{\text{Cacyt}}\right)^4+\left(\frac{\text{Cacyt}}{\text{Kb}}\right)^3}$$

$$\tau[\text{Cacyt}] = W^{\infty}[\text{Cacyt}]/(\text{Kc}-) \ldots\ldots(3)$$

$$\frac{dw}{dt} = -(W - W^{\infty}[\text{Cacyt}])/\ \tau[\text{Cacyt}] \ldots\ldots.(4)$$

Popen is proportional to W=1-C2 (not in state C2), that is equal to C1+O1+O2, which is the fraction of non-inactivated receptors.[25] In Keizer and Levine model, to simplify the model, Value of W is fixed to 0.963 near to its initial value.[24] Ka and Kb are rate constant and it plays vital role in Ryanodine channel sensitivity for its opening, Cacyt is cytosolic calcium concentration.

2.2 **Flux**

Flux is gradient that pass through the receptor.

Here in this governing equation, Caer (calcium concentration in endoplasmic reticulum) is given by [Keizer and Levine, 1996]

Caer= (Co-Cacyt)/c1 ……(5)

Where, Co is calcium concentration in cell, c1 is effective volume of endoplasmic reticulum to that of cytoplasm

In that flux through Jryr is given by

Jryr = V1.Popen.(Caer- Cacyt) ……..(6)

Where V1 is maximum Ryr channel calcium permeability, from equation (1) Popen is the sum of the fraction of channels in the RyR channel open states O1 and O2. Caer and Cacyt is the calcium concentration in endoplasmic reticulum and in cytoplasm, respectively, and difference between them act as driving force for the release of calcium from Ryr.[20]

As shown in table 1, value of rate constant is mentioned which is tuned to get required simulation. Cytosolic calcium concentration vary from 0.1 to 0.9 µM. In Ryr flux, calcium in cell concentration is tuned from 100 to 110 µM.

Table 1 Cardiac Open probability

Parameter	**Symbol**	**Value**	**Ref.**
Ryanodine rate constant	Ka	$0.0192\mu M^4$	[24]
Ryanodine CICR rate constant	Kb	$0.2573\ \mu M^3$	[24]
Ryanodine rate constant	Kc	0.0571	[24]
Ryanodine rate constant	Kc-	$0.1S^{-1}$	[24]
Cytosolic calcium	Cacyt	0.1to0.9µM	[24]

Table 2 Neuron Open probability and Flux

Parameter	**Symbol**	**Value**	**Ref.**
Ryanodine rate constant	Ka	$7.2\mu M^4$	Tuned
Ryanodine opening rate constant	Kb	$6.02\mu M^3$	Tuned
Cytosolic calcium	Cacyt	0.1to100µM	[22]
Flux from Ryr(Jryr)			
Maximum Ryanodine channel calcium permeability	V1	0.05/ms	[24]
calcium in the cell	Co	100 µM (tuned to 110 µM)	[24]
Weighted volume fraction	c1	0.02	[24]

Intracellular calcium is maintained by channel at plasma membrane and ER. However, in AD, as intracellular calcium level increases, there is increase in open probability, expression of Ryr and also flux from Ryr at ER increases. These increase in calcium found at early state of AD. So, there is alteration in calcium level and channel in simulation, which can be compared with normal.

Intracellular calcium is maintained by channel at plasma membrane and ER. However, in AD, intracellular calcium level increases, there is increase in open probability, expression of Ryr and also flux from Ryr at ER increases. These increase in calcium release from Ryr found at early state of AD. So, there is alteration in calcium level and channel in simulation, which can be compared with normal.

RESULT AND DISCUSSION

3.1 Cardiac Open Probability

The Open Probability is opening of channel and gradient that pass through it, is flux. In figure 3, Keizer and Levine modelled Ryanodine receptor open probability versus cytosolic calcium concentration for cardiac. In order to, to study open probability behaviour of Ryanodine receptor, in figure 3a Popen Vs Cacyt is simulated on MATLAB, which is replica of Keizer And Levine model.[24]

In figure 3, in both simulation, Popen vary between 0 and 1. Cytosolic calcium concentration 0.1µM act as threshold, which is same for both results. When it cross the threshold , Popen increases, there is quick response to rising of calcium, upon further increase in cytosolic calcium, it cause Ryanodine to further increase in Popen and subsequently it reach maximum at 1 µM cytosolic calcium concentration. Afterwards, with increase in cytosolic calcium, it results nearly identical rise in open probability of Ryanodine receptor.

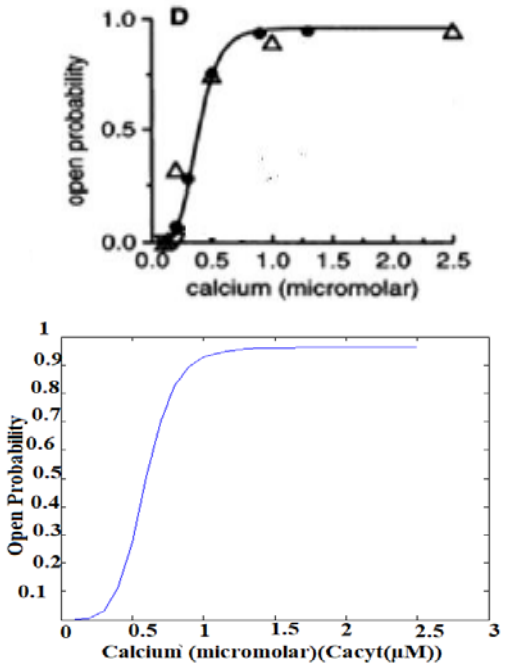


Figure 3 a) Keizer and Levine, Cardiac Ryanodine open Probability vs Cytosolic, Filled circle represents data from simulation[Keizer and Levine, 1996] (b) MATLAB simulation result for cardiac ryanodine open Probability

3.2 Neuron Open Probability

For neuron Ryr, same Keizer and Levine model equation is used to obtained open probability of Ryr channel. Here, in figure:4 open probability used to get increased rapidly, at 1 to 10 µM cytosolic calcium concentration. Then after, further increase in cytosolic calcium concentration open probability gets saturated and produce identical rise in open probabilty (Popen). In this figure also W which is not in C2 state, determines Popen value.

In figure 4, At low cytosolic Ca^{2+}, RyR channels are closed, with extremely low open probability (Popen). The Popen increases at submicromolar levels of cytosolic Ca^{2+}, reaching a maximal Popen at 10 µM.

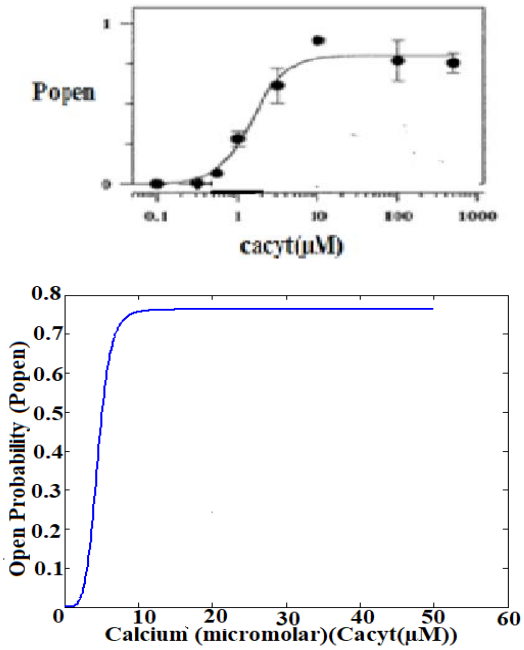
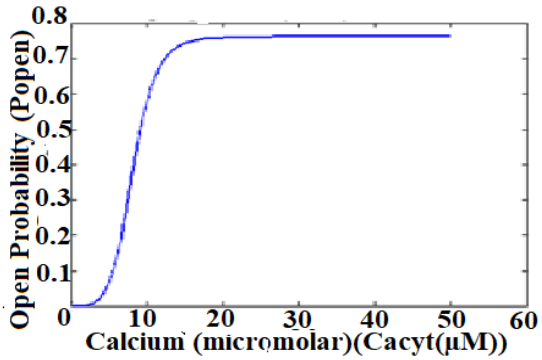


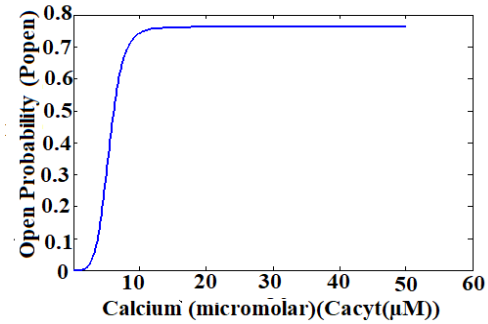
Figure 4. Open Probability Vs Cytosolic calcium concentration a)Rat Brain cortex, Ryr open Probability[5] b) Simulation result for neuron Ryanodine open probability

Here, in simulation, we got result based on selected parameter, so our main aim is to determine the parameter which plays crucial role in simulation, and by varying that particular parameter we can get simulation for different condition and disease, and we can deduce about that particular parameter, which generally results in changes in that simulation, so that parameter will require to be controlled for further application whether its therapeutic or pharmaceutical.

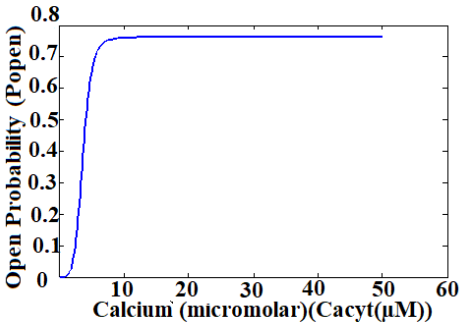
In figure 5, Open Probability (Popen) is simulated versus cytosolic calcium concentration for different value of Ka and Kb(parameter), which are gating mechanism of Ryanodine receptor.



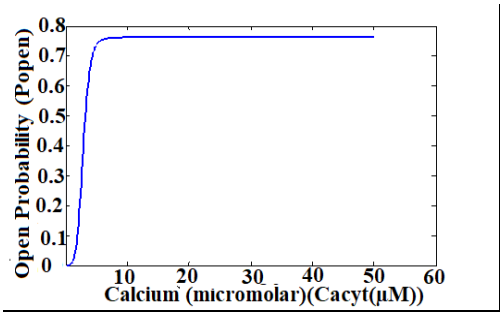
(a) Ka=9.28, Kb=9.04



(b) Ka=6.2, Kb=6.02



(c) Ka=4.2, Kb= 4.02



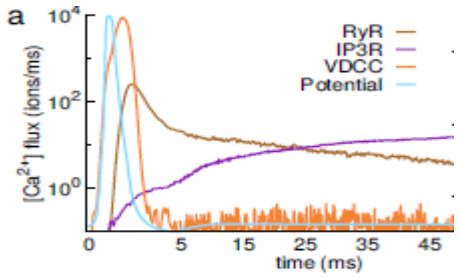
(d) Ka=3.2, Kb= 3.02

Figure 5. Simulation: Open Probability of Neuron Ryr at different rate constant, Ka & Kb.

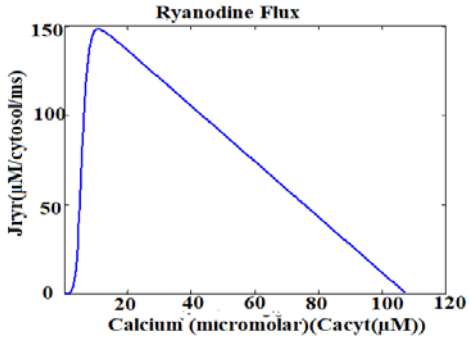
In the figure 5, relaxation value W, which is not in C2 state, determines Popen value. Ka vary the activation sensitization of Ryanodine. Kb used to bend the curve. On the decreasing the Ka value Ryanodine sensitization increases, its hreshold value decreases, and at low cytosolic calcium value Popen increased. W relaxation constant, controls Popen. Popen vary between 0 and 1.

3.4 Neuron Ryanodine Flux Simulation

In figure 6b calcium flux of ryr channel is plotted vs Cytosolic calcium, as per figure ryanodine is having fast activation and slow inactivation, mean with slight increase in cytosolic calcium concentration, flux from Ryr increases . A fast increase of cytosolic calcium is lagged by a strong calcium release flux from ryr, and on further increase in cytosolic calcium, ryr flux starts decreasing (move down slowly) and the shape become similar to concentration, flux from Ryr increases . A fast increase of cytosolic calcium is lagged by a strong calcium release flux from ryr, and on further increase in cytosolic calcium, ryr flux starts decreasing (move down slowly) and the shape become similar to spike, so, calcium release phase is maximized. In figure:6 b) is flux simulation for Ryr neuron where flux increases, till 10micromolar cytosolic calcium concentration and ryr channel tend to close beyond 100 micromolar cytosolic calcium concentration, and flux through Ryr channel become zero as ryr channel closed.



(a) CA3 neuron Ryr Flux Vs time[12]



(b) Simulation neuron Ryr Flux Vs Cacyt

Figure 6. Neuron Ryr flux

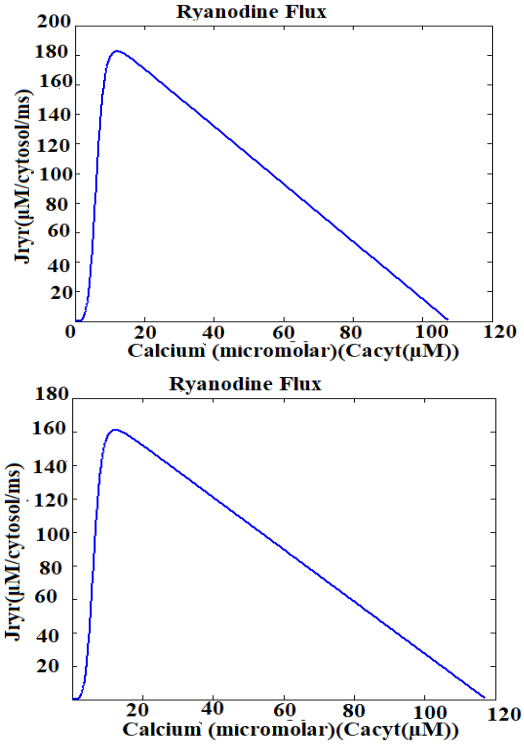
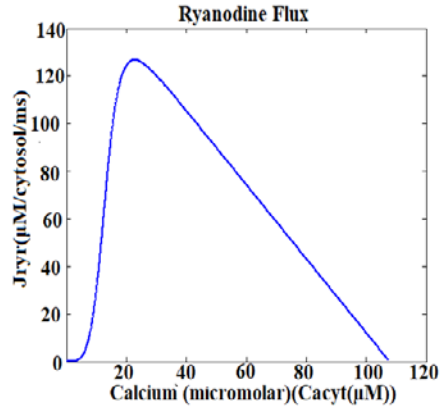
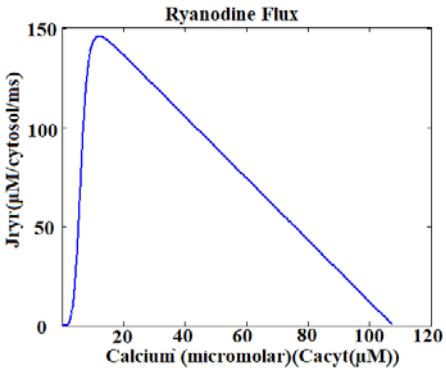


Figure 7. Simulation of Ryr flux Vs Cacyt a) At V1=0.05 has increased amplitude of flux, from 140 to 180 b) At Co= 120 shifts the closing of Ryr to 120 also increase the amplitude to from 140 to 160.

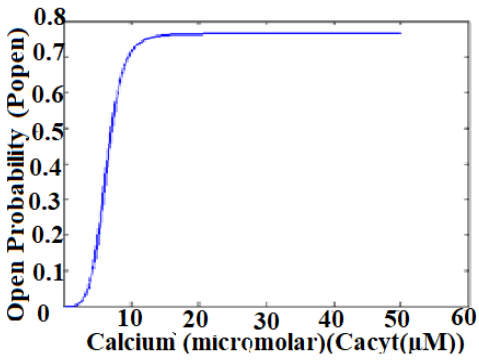


At Ka=15.2, Kb=15.02

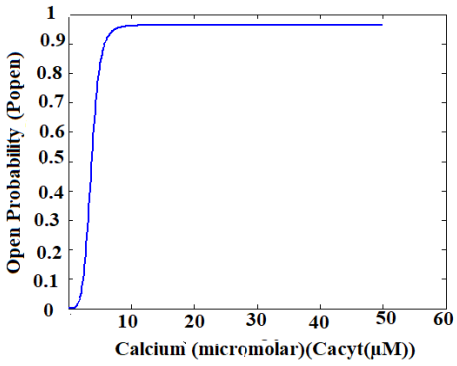


Ka=7.2, Kb=6.02

Figure 8 Simulation of Ryr flux Vs Cacyt



(a) **Ka=7.2, Kb=6.02**



(b) Ka=4.2 , Kb=4.02

Figure 9. (a) For Normal Ryr Popen (b) for AD

In this figure: 6 b) parameter Ka and Kb in flux controls activation (threshold for activation) , V1 controls amplitude of Jryr and Co determines the width of spike that is inactivation value. So, Ryr flux amplitude compared with experimental figure:6 a) CA3 neuron Ryr flux, and plotted.

In Figure 7 a), V1 channel permeability , determines Ryanodine Flux. So when value of V1 is increased then flux from Ryr increased. Co is, calcium in the cell, vary the closing of Ryanodine channel. On increasing the Co value, the Ryanodine closed at 120 micromolar cytosolic calcium concentration from 110 micromolar, as we compared the figure 7b with figure 7a.

In Figure 8, Ryr flux is plotted at different value of Ka and Kb. In figure 6 a, which is plotted at Ka=15.2, Kb=15.02, on increasing its value, it decreased the sensitization and it shifts the curve right as we compared the figure 8a with figure8 b.In Alzheimer, here is increase in expression of ryr i.e it sensitised the ryr open probability

towards low cytosolic calcium concentration. That means the parameter that got affected is

Ka and Kb. In addition, there is increase in open probability of Ryr, so W increased, which is not in state C2. So, Alzheimer increase its expression towards low cytosolic calcium concentration. That means the parameter that got affected is Ka and Kb. In addition, there is increase in open probability of Ryr, so W increased, which is not in state C2. So, Alzheimer increase its expression.

In figure 9 relaxation constant i.e w determines the Popen value, so I increased thevalue upto 0.963. From ka sensitivity of channel, so I decreased the value of ka , so at lowcytosolic calcium its expression increases. kb it used to bend the curve . So I decreased the value.

4. Conclusion

Alzheimer, which is neurodegenerative in nature, starts at hippocampus of temporal lobe, led to dementia. There is no treatment available so far, for Alzheimer 's Disease. Hallmark of Alzheimer is presence of neurofibrilliary tangles, however, prior to it, there is alteration in intracellular calcium formation, which is vital for Long term potentiation, neurotransmitter release and many more. There is increase in intracellular calcium level concentration, that led to cell apoptosis.

Inside cell, intracellular calcium is maintained by channel, which are present on plasma membrane and some are on endoplasmic reticulum. Intracellular calcium increased by channel, which are present on plasma membrane, is further amplified by channel, that is Ryanodine and Ip3, upto required level. Ryanodine plays important role in Long term potentiation, neurotransmitter release, action potential shape.

In Alzheimer, there is increase in expression, open probability of ryanodine receptor. At slight low cytosolic calcium concentration, there is increase in open probability of ryanodine receptor. Ultimately, that led to increase in flux of Ryanodine channel.

ACKNOWLEDGMENTS

Authors acknowledge the support provided by the GEC Gandhinagar Biomedical Engineering Department.

CONFLICT OF INTEREST STATEMENT

Authors declare that there is no conflict of interest in publishing of this research work.

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