

Review on Modelling Aspect of Ryanodine Receptor in CA1 Neuron

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Abstract: Alzheimer is a neurodegenerative disease, which is most prevalent in worldwide. But there is no cure for it so far. From many reasons, elevated calcium concentration is one, that has their roles in this disease, and it starts at early stages. According to studies, Ryanodine receptor (RyR) can be targeted for further studies, for early detection of Alzheimer's disease (AD) and for therapeutic drug for treatment, since alteration in intracellular calcium concentration caused by many channels, among them one of them is increase in expression of RyR, which increases the calcium flux at intracellular level. Also based on calcium induced calcium release, it activates its neighbouring RyR as well. So there is up regulation in intracellular calcium concentration, which deteriorates memory process. In addition, it affects action potential (shape) by the activation of large conductance channel, since it plays a vital role in neurotransmitter release. In later stage, apoptosis takes place (neuron cell death) which is characterised by increase in memory loss (so neural connection decreases). Further, this Alzheimer starts in hippocampus, where there is significant reduction of neuronal density, especially in CA1 neurons. This occurs at an early stage of disease. In this paper we have explored the Ryanodine and their mechanism in neuron.

Keywords- Alzheimer, neurodegenerative disease, Calcium, Ryanodine receptor, calcium induced calcium release

(I) INTRODUCTION

Hippocampus plays a vital role in memory formation. Generally, Cornu ammonis (hippocampus proper) and dentate gyrus are the two parts of hippocampus. But, by some of the anatomists, hippocampus has divided into Hippocampus proper (Cornu ammonis), dentate gyrus, subiculum, and entorhinal cortex (EC) area. Hippocampus proper (Cornu ammonis) is further divided into CA1, CA2, CA3, and CA4 based on histology. In that, CA1 plays a critical role in contextual and autobiographical memory retrieval, re-experiencing detailed episodic memories. It is also responsible for Long term potentiation (LTP). CA1 contains pyramidal cells, which are named due to their shape, they mediate cognitive functions. So, CA1 is the region, plays a role in new memory formation and strengthens the memory [1,2,3].

(A) Alzheimer's Disease

Alzheimer's Disease (AD) which is neurodegenerative, results in memory impairment and affects mainly elderly people. This happens because neurons, which are

responsible for cognitive function, get damaged, so, they diminish cognition, memory, language, and is defined by the presence of dementia [4]. The hallmark of the disease is defined by the presence of extracellular amyloid β ($A\beta$) plaques and intracellular neurofibrillary tangles (NFTs) containing hyper-phosphorylated tau, which in normal conditions holds the microtubule protein together, acts as a road for the transport of intracellular nutrients, however, in AD transport of nutrients is blocked by NFT, and cell death occurs [5].

Hippocampus is linked with memory formation, so the first degenerative process starts in hippocampus, under AD, hippocampus begins shrinking (atrophy) [6]. Then degeneration proliferates all over the temporal associated cortex, parietal areas. As AD grows, frontal cortex gets affected. It causes profound damage on various components of the limbic system [7,8]. In AD, there is significant reduction in neurons in CA1, CA3 hippocampal area, however, as per the analysis, there is huge loss in CA1 neuron density, in comparison with other levels [9].

At cellular level, Calcium ion being a second messenger, plays a vital role in physiological functions [10], in brain, these are neurotransmitter release, action potential, memory formation [11]. So, fluctuation in calcium concentration beyond the required level, results in pathogenesis i.e. neurodegenerative disease, Alzheimer's disease [12], also perturbation in calcium concentration, occurs in advance of neuron cell death and cognitive decline in Alzheimer [13]. Further, in Alzheimer, ryanodine receptor (RyR) expression at intracellular level, rises with early cognitive decline and neurofibrillary pathology, and at late stage, it is reduced in CA1-CA4, subiculum regions [14].

The calcium inside the cell is maintained and regulated by some channels located on plasma membrane, endoplasmic reticulum and mitochondria. Here, in neuron, rise in calcium level results in neurotransmitter release at synaptic cleft, that contributes towards synaptic plasticity as well as action potential [15,16]. Endoplasmic calcium at dendrites plays roles in post synaptic process and synaptic plasticity [17] and at axon in neurotransmitter release [18]. Calcium concentration is maintained at different levels like 2mM in extracellular space, cytosolic is 100nM [19]. Variation in intracellular calcium concentration underlies cellular mechanisms of learning and memory (synaptic plasticity), include Long term potentiation (LTP) and long

term depression(LTD). High calcium concentration spike triggers LTP, in that during certain phase of sleep, information consolidate to permanent memory from temporary memory. Small rise in calcium activate Long term depression(LTD) during another phase of sleep, that erases temporary memory. While in AD, permanent rise in calcium erases temporary memory, before it can be transferred to permanent memory[20]. So, change in the level of intracellular calcium get involved in brain activity, including learning and memory and memory loss precedes the massive cell loss[21].

(II) LITERATURE SURVEY

In Fig.1:(A), in response of , neurotransmitter releases from presynaptic axon terminal, influx of calcium takes place from voltage gated calcium channel(VGCC) at post synaptic terminal, during depolarization[22,23]. Then calcium interact with RYR, caused it to get open, efflux of calcium from endoplasmic reticulum takes through this channel[24].

The second major intracellular calcium channel is Ionsitol triphosphate(IP3), is ligand gated IP3 channel. External stimuli acts on G-protein , which activates phospholipase C, and generate IP3, IP3 diffuse from plasma membrane to endoplasmic reticulum, binds to and opens ligand gated ion channel, Calcium moves out from the endoplasmic reticulum into the cytosol, which stores calcium , and it activates various cellular function. However, mitochondria takes up the calcium using mitochondria calcium uniportar (MCU). Sodium/calcium exchange(NCX) moves the calcium out of cytoplasm[25].

There is other calcium influx pathway, SOCC(store operated calcium channel), which activated when ER calcium depleted. In that STIM which sits in the ER membrane, forms clusters, closure to the plasma membrane, interacts with Orai, forms a calcium channel to allow calcium influx from extracellular medium. Also, depleted ER calcium store, refilled by sarco/endoplasmic reticulum ATPase pump(SERCA) pump[25].

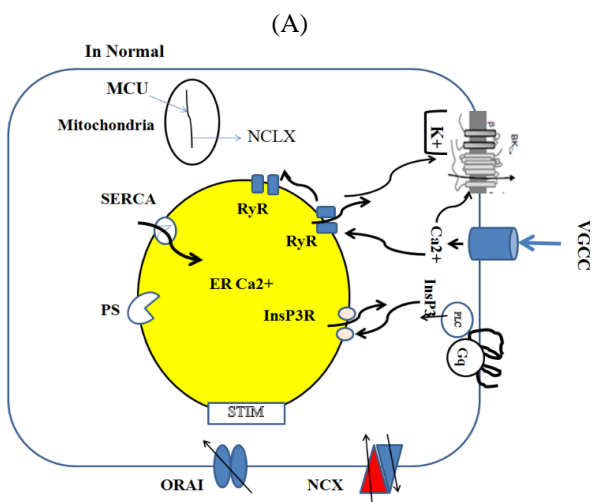


Fig 1:(A) intracellular mechanism in normal neuron

Then increase in level of intracellular calcium ,during action potential depolarization led to activation of calcium activated potassium channel, situated near VGCC[26]. Ultimately, efflux of potassium ion and closure of calcium channel takes place and it produce after fast hyperpolarisation[27]. So, it contributes in maintenance of shape and duration of action potential [28].

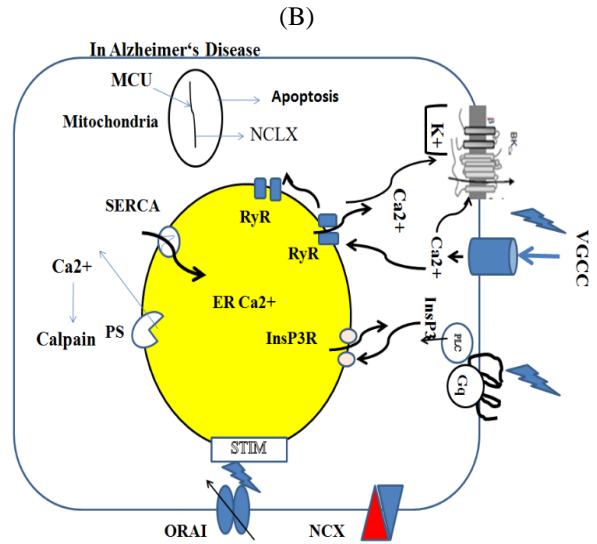


Fig.1(b) intracellular mechanism in Alzheimer

It is important to have proper balance in calcium haemostasis, for neuronal survival and memory formation(synaptic plasticity). However, In AD, in fig.1(b) there is increase in VGCC, by which calcium influx rises[29]. Ryanodine also works with increase in its expression[30,31,32] Presenilin acts as leak channel [33] and it also alters the normal function of SERCA[34]. Also, gating of IP3 increases, due to interaction of Presenilin with IP3 receptor[35] and stimulation of mGluR receptor linked with IP3 production[36]. In addition depletion of Endoplasmic reticulum calcium, activates Store operated calcium entry via the STIM/ ORAI pathway[37]. And efflux of accumulated intracellular calcium level via Sodium/ calcium exchange(NCX) gets inhibited in Alzheimer condition[38]. Increase calcium cause excessive flux into the mitochondria that increases its overload, generation of superoxide radicals, caspases and cytochrome C, that led to cell death(Apoptosis)[34].

In addition, raised intracellular calcium level affects LTP[34] and Action Hyperpolarisation, which are result of calcium activated potassium channel[39]. Also, increased calcium level, increased activity of calpain, which in turn led to Tau hyperphosphorylation[40]. So all might ultimately contributes towards later stages of disease, that is cell loss. So under AD, malfunctioning of these channel, results in increased intracellular calcium level and it has deleterious effects on the functioning of cell.

Membrane permeability to potassium ion, which is vital for neurotransmitter release and many other cellular function is controlled by intracellular calcium[41]. In hippocampal

pyramidal neuron, ryanodine receptor are present at higher level, which is activated through calcium influx from VGCC, followed by calcium induced calcium release(CICR), which dominate in CA1 neuron for ryanodine receptor[42], so there is link between AHP and calcium release from Ryanodine receptor. Also, Ryanodine receptor on stimulation, enhance memory process[43] and on blockade RYR, in mouse model it reduce memory impairment[44], however, it induce amnesia[45].

(III) MATHEMATICAL FORMULATION AND ANALYSIS

Here, the author has conduct research on RYR in cardiac myocytes, to find RYR adaptation. With increase in calcium concentration, open probability of ryanodine channel increases.

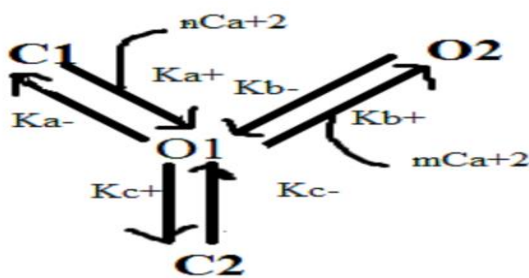


Fig 2 transition among four state of RYR. step a and b is only calcium dependent[46].

In fig.2 C1 and C2 are two closed state, where as O1 and O2 are open state. At low calcium concentration it is C1 states. In transition state, state C1 to O1 and O1 to O2 are calcium dependent, which depends on binding of n and m calcium ion respectively. The step in the absence of O1 to C2 are considered to be CICR. On slow transition from O1 to C2 it exhibits inactivation. when we translate the schematic diagram into kinetic equation using mass action law then differential equation can be written as follows :-

$$\frac{dP_{C1}}{dt} = -K_{a+}[Ca^{2+}]^n P_{C1} + K_{a-} P_{O1} \quad (1)$$

$$\frac{dP_{O1}}{dt} = K_{a+}[Ca^{2+}]^n P_{C1} - K_{a-} P_{O1} - K_{b+}[Ca^{2+}]^m P_{O1} + K_{b-} P_{O2} - K_{c+} P_{O1} + K_{c-} P_{C2} \quad (2)$$

$$\frac{dP_{O2}}{dt} = K_{b+}[Ca^{2+}]^m P_{O1} - K_{b-} P_{O2} \quad (3)$$

$$\frac{dP_{C2}}{dt} = K_{c+} P_{O1} - K_{c-} P_{C2} \quad (4)$$

O2 states corresponds to plateau open probability increasing. K_{i-}^{+} are rate constant, a & b is fast(millisecond time scale and C is slow (second time scale. P C1 is RYR fraction that is state in C1. From $\frac{dP_c}{dt}$, we can deduce that how this vary with time.

The equation for Ppeak open probability is given by[46]
 $P_{peak}([Ca^{2+}]) = (W_{inf}(0.1\mu M) + ([Ca^{2+}]/K_b)^3) / (1 + (K_a/[Ca^{2+}])^4 + ([Ca^{2+}]/K_b)^3) \quad (5)$

where $W_{inf}(0.1\mu M)$ is the equilibrium value of 1- P_{c2} evaluated at the initial value $[Ca^{2+}] = 0.1\mu M$

Plateau value of P_o is equilibrium value of $P_{o1} + P_{o2}$ and it can also be written as P_{open} . So, Open Probability(P_{open}) of Ryanodine receptor (normal) from Keizer and Levine is given by[46]

$$P_{open} = W / ((1 + (\frac{c}{K_b})^3) / ((1 + (\frac{K_a}{c})^4 + (\frac{c}{K_b})^3)) \quad (6)$$

where $W = 1 - C_2$, fraction of channel not in state C2, K_a and K_b are kinetic parameter. W determine the rate of relaxation to its plateau[47].

$$J_{ryr} = V_{ryr} \times P_{open} \times (S - C) \quad (7)$$

The driving force for the flux is Endoplasmic Reticulum membrane calcium gradient is (S-C) [47]

Herein , AD, open probability of ryanodine receptor increases. In the absence of external calcium fluxes (closed cell model) the mechanism led to bistability.

kinetic model of Ryanodine receptor is used to describe CICR from internal store. This is combined with a passive leak and SERCA pump that returns calcium to the store[46].

$$\frac{dc}{dt} = (V_1 \cdot P_{open} + V_2)(S - C) - (V_3 * (\frac{C^2}{C^2 + K_3^2})) \quad (8)$$

Table:1 Simulation parameter

Property	Value	Reference
Kinetic parameter, K_a	0.372 μM	47
Kinetic parameter, K_b	0.0636 μM	47
K_c , kinetic parameter	.0571	47
V_{ryr}	$10^{-6} cm/ms$	47
C (calcium concentration in cytosol)	0.1 to 0.9 μM	46
S (calcium concentration in ER)	250 μM	49

Table:2 Parameters for closed cell

Parameter	Value	Meaning	Reference
V_1	40 s ⁻¹	Rate constant for RYR	(47)
V_2	0.5 s ⁻¹	Rate constant for store leak	(47)
V_3	1000 $\mu M s^{-1}$	Maximal rate of SERCA Pump	(47)
K_3	0.30 μM	Dissociation constant for SERCA	(47)

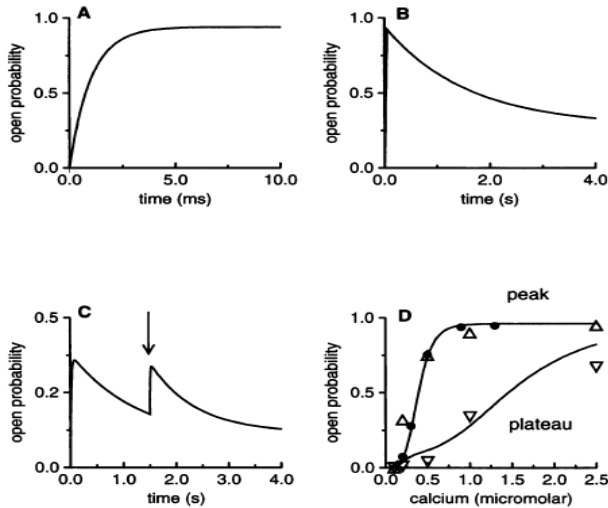


Fig.3 Variation in Ryanodine open probability with time and calcium[46]

Fig. 3A is $P_o = P_{o1} + P_{o2}$, where calcium varies from 0.1 to 0.9 μM . Activation takes place in milliseconds while decline to plateau in seconds. In Fig. 3B, inactivation occurs on a second scale. Fig. 3C shows the first variation in calcium ions from 0.1 to 0.35 at $t = 0$, followed by enhancement up to 0.50 μM . Fig. 3D shows the peak and plateau that depend on calcium, with solid curves as theoretical values and experimental data points (upward triangles for peak, downward for plateau) [46].

Another RYR model with no time dependence or gating kinetics was constructed by Friel (1995). This calcium model is based on calcium oscillation in sympathetic neurons [48].

Here, flux is proportional to concentration difference

$$J_{ryr} = K3(C_e - C)$$

where C_e and C are ER calcium concentration and cytoplasmic calcium concentration respectively. And

$$K3 = k1 + \frac{K2C^n}{(Kd^n + C^n)}$$

where $n=3$, the first factor $K3$ is open probability, where $K1$, $K2$ and Kd are parameters. The parameter $K1$ is the zero calcium concentration level leak. Kd corresponds to RYR channel sensitivity for calcium-induced calcium release (CICR), and $K2$ is the maximal rate of channel [48].

$$K1 = 0.013s^{-1},$$

$$Kd = 0.13\mu\text{M} \quad K2 = 0.18s^{-1}$$

(IV) CONCLUSION AND FUTURE SCOPE

This review paper attempts to explain what generally happens at intracellular calcium signaling in Alzheimer.

In AD, there is up-regulation in calcium at intracellular level by internal stores and extracellular mechanism. Among them, this review focused on Ryanodine receptor, in which there is an increase in expression of ryanodine

receptor, that is open probability of ryr increases. In addition, Ryr involves in memory process, and calcium released via this channel takes part in action potential. So, in future, model will focus on Ryr open probability and from them we can drive flux and current.

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