Published in final edited form as:

Drug Discov Today Dis Models. 2016 ; 19: 37–42. doi:10.1016/j.ddmod.2017.02.005.

Capturing intracellular Ca^{2+} dynamics in computational models of neurodegenerative diseases

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Abstract

Many signaling pathways crucial for homeostatic regulation, synaptic plasticity, apoptosis and immune response depend on Ca^{2+} . Ca^{2+} dysregulation disrupts normal function of neurons and neuronal networks. This causes severe motor and cognitive disabilities. Understanding how Ca^{2+} dysregulation triggers disease onset and progression, and affects downstream processes, can help identify targets for treatments. Because of intermingling of molecular pathways, dissecting the role of individual mechanisms and establishing causality is very challenging. Computational models provide a way to decipher these processes. I review some computational models with Ca^{2+} dynamics to illustrate their predictive power, and note where extending those models to capture multiscale interaction of Ca^{2+} dependent molecular pathways can be useful for therapeutic and drug discovery purposes.

Introduction

Proper handling of intracellular Ca^{2+} is essential for excitability, homeostatic regulation, synaptic plasticity, pathogenesis and apoptosis. A complex network of Ca^{2+} regulatory machinery maintains the cytosolic Ca^{2+} levels within a physiological range over the life span of the neuron. Improper handling of Ca^{2+} can destabilize the homeostatic process, alter the network connectivity patterns, and can eventually lead to neuronal death. Although the malfunctioning of Ca^{2+} regulatory mechanisms is typically observed in all of the neurodegenerative disorders, the process that triggers the disease onset and cause malfunctioning of Ca^{2+} regulatory mechanisms is not understood. Computational models with Ca^{2+} regulatory mechanisms and Ca^{2+} -dependent signaling pathways can help establish the basis of disease onset and progression and eventually could allow uncovering targets for drug delivery. Here I review a few computational models of neurodegenerative diseases with emphasis on Ca^{2+} dynamics and argue how those models can be extended to be used for treatment of neurodegenerative diseases.

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Conflict of interest statement

Nothing declared.

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Ca²⁺ dysregulation in neurodegenerative diseases

The onset of many neurodegenerative diseases is believed to be triggered by abnormal aggregation of intracellular and extracellular toxic proteins such as beta amyloids (A β) in Alzheimer and α -synuclein in Parkinson. The aggregation of these proteins disturbs the homeostatic regulation by altering the dynamics of Ca²⁺ regulatory mechanisms in healthy cells. In Alzheimer, A β could self-aggregate into oligomers, which in turn could then either enhance Ca²⁺ leak from endoplasmic reticulum (ER) into cytosol [1] or enhance mitochondrial-ER cross talk via mitochondria-associated ER membranes (MAMs) [2]. Similarly, α -synuclein in Parkinson may enhance plasma membrane permeability to Ca²⁺, which could increase Ca²⁺ levels in cytosol and other cytosolic organelles [3]. Extracellularly, A β could block K⁺ channels and lower the threshold of spiking. This enhances the excitability of the neuron and can cause significant increase in intracellular Ca²⁺ levels [4]. Moreover, protein aggregation and misfolding could directly or indirectly affect the Ca²⁺ permeability of voltage-gated Ca²⁺ channels (VGCCs), AMPARs and NMDARs, or could result in decreased affinity of plasma membrane Ca²⁺-ATPases (PMCA), sarco/endoplasmic reticulum Ca²⁺-ATPases (SERCAs), Na⁺-Ca²⁺ exchangers (NCXs) and Ca²⁺ buffers. Handling increased loads of Ca²⁺ and breakdown of increased toxic proteins could cause oxidative stress [5] and might trigger autoimmune [6] response leading to homeostatic imbalance, loss of network connectivity and neuronal death.

In Parkinson, dopamine-releasing neurons within substantia nigra (SN-DA) are particularly vulnerable to degeneration compared to other dopaminergic neurons. The Ca²⁺ regulatory mechanisms are not only crucial for dopamine release within a physiological range but also modulate mitochondrial [7] and lysosomal activity [8], their metabolic stress levels, and their vulnerability to degeneration. Because of low levels of Ca²⁺ binding proteins like Calbindin (CB) in SN-DA neurons, Ca²⁺ is mainly removed from cytosol by uptake into ER via SERCA pumps and by mitochondria via mitochondrial Ca²⁺ uniporter (MCU) or mitochondria Ca²⁺/H⁺ exchanger or indirectly via MAMs. This complex intrinsic configuration of Ca²⁺ regulatory mechanisms make SN-DA neurons more vulnerable to any imbalance of Ca²⁺ levels and could easily trigger disease onset.

In Huntington, striatal spiny projection neurons are considered to be the main target for disease onset. In addition to synaptic dysfunction in these neurons, Huntington disease gene (Htt) alters Ca²⁺ homeostatic regulation by disrupting mitochondrial and ER function. Htt directly interacts with the mitochondrial membrane reducing its ability to sequester Ca²⁺ [9]. Bezprozvanny and colleagues showed that mHtt sensitized the Inositol triphosphate receptors (IP₃R1s) to IP₃, thereby enhancing Ca²⁺ release in response to activation of metabotropic glutamate receptors [10]. Subsequent studies indicated that inhibition of IP₃R1 function by genetic knock-down, interfering peptides or pharmacological agents could protect striatal neurons from glutamate-mediated apoptosis [11,12]. In a recent study, Bezprozvanny group showed that striatal dendritic spine loss could also be rescued by inhibition of the store operated Ca²⁺ entry (Ca²⁺ entry through plasma membrane Ca²⁺ channels like transient receptor potential - TRP channels in response to depletion of ER Ca²⁺), which is observed to be over-active in response to a depletion of ER Ca²⁺ stores because of the higher basal activation of IP₃R1 induced by mutant Htt [13]. Ryanodine

receptors (RyRs) mediate Ca^{2+} -induced Ca^{2+} release in response to influx through plasma membrane channels; however, RyR can also act as a source of Ca^{2+} “leak” into the cytosol at rest elevating the basal intracellular Ca^{2+} concentration [14]. In neurons, such chronic increases in intracellular Ca^{2+} can alter responsiveness of a large number of signaling pathways, shifting threshold for synaptic plasticity, survival/growth, and other signaling essential for the neurons’ role in circuit function.

Mitochondrial dysfunction and alteration in ER-mitochondria crosstalk are thought to be primarily involved in Ca^{2+} dysregulation in ALS affected motor neurons [15] (also see review [16]). Excessive mitochondrial Ca^{2+} accumulation can cause the opening of the mitochondrial permeability transition pore, which has been associated with activation of cell death pathways [17]. It was demonstrated experimentally that altering the physical distance between the opposing membranes affect Ca^{2+} flow from ER to mitochondria and cell viability [18]. The most evident ER abnormality described in ALS is ER stress accompanied by upregulation of the unfolded protein response (UPR). This phenomenon has been amply described in ALS patients [19], as well as in cellular and animal models of ALS [20,21]. However, it is unclear what exactly triggers the activation of UPR. It is likely that proteostasis dysregulation is involved in the activation of UPR. The experimental evidence suggests that MAMs and ER-mitochondria communications, especially lipid metabolism and Ca^{2+} signaling between the two organelles, are logical points of interaction in the pathogenesis of different forms of ALS. Decreased ER-mitochondria interaction could result in insufficient Ca^{2+} transfer from the ER stores to mitochondria and defective bioenergetic coupling. It could also alter the autophagic process, because of impaired vesicle biosynthesis. However, abnormally increased or persistent ER-mitochondria contact might result in enhanced Ca^{2+} flux into mitochondria, triggering mitochondrial permeability transition and apoptosis. RyRs could also be potentially dysregulated in ALS causing abnormal cytosolic and mitochondrial Ca^{2+} influx [22]. Sensitivity to Ca^{2+} dysregulation may be affected by Ca^{2+} binding proteins, since motor neurons have lower amount of these proteins compared to ALS-spared neurons [23].

Computational models of neurodegenerative disorders with Ca^{2+} dynamics

As described in previous section, it is evident that the impact of neurodegenerative disorders on Ca^{2+} dysregulation is multiscale. However, most of the computational models of neurodegenerative diseases developed in the past considered a single factor. For example, some models only focused on understanding the dynamics of proteins aggregation underlying neurodegeneration [24–27], whereas the others focused on understanding how an individual subcellular organelle and its associated pathways function under normal and diseased condition [28]. The dynamics of Ca^{2+} , which mediates disease onset, disease propagation and control homeostatic regulation, signaling pathways and apoptosis, were either completely ignored or included with minimal details. At network level, the mechanisms of synaptic dysregulation and their effects on network connectivity and homeostatic regulation were only explored at phenomenological level [29–31].

Although those single-factor models provide useful insights into brain disease, the pathological consequences necessarily end up being attributed to a single factor that was

picked out to be explored in the model. Such self-confirmatory results are not incorrect; typically the factor being explored *is* of importance. However, as noted above neurodegenerative diseases cause disruption of many interacting processes. Therefore, detailed multiscale mechanistic computational models of neurodegenerative diseases with excitability, detailed dynamics of Ca^{2+} regulatory mechanism and Ca^{2+} dependent signaling pathways would be more useful. A few computational models of neurodegenerative diseases with Ca^{2+} dynamics captured at different scales are briefly described below. These examples show how simple computational methods can be used to understand the disease mechanisms and if extended to include more details can provide a powerful tool for therapeutic and drug discovery purposes.

An example of a computational model of protein aggregation was developed by De Caluwe and Dupont [32]. Their model qualitatively described the interactions between intracellular Ca^{2+} and $\text{A}\beta$. The rise and decay of intracellular Ca^{2+} and $\text{A}\beta$ level were captured by a single rate constant for each. The activation of $\text{A}\beta$ synthesis by Ca^{2+} was represented by a Hill term with a maximal rate V_a , half-saturation constant K_a , and a Hill coefficient n . They also considered that $\text{A}\beta$ oligomers induce Ca^{2+} entry into the cell, putatively by provoking an increase in plasma membrane permeability. This process was characterized by a cooperativity coefficient m , and a rate constant k_β . Using that model the authors showed that a ‘steady state’ characterized by low levels of Ca^{2+} and amyloids, coexist with ‘pathological state’ where the levels of both compounds are high. Thus, a large enough perturbation in either amyloid metabolism or up regulation of Ca^{2+} homeostasis could trigger AD onset.

Both experimental and computational modeling studies have shown how $\text{A}\beta$ -mediated alteration of Ca^{2+} regulating mechanisms can cause increased cytosolic Ca^{2+} levels in patients with Alzheimer’s disease. For example, Good et al [4] showed in cultured hippocampal neurons that $\text{A}\beta$ could block fast inactivating K^+ currents without affecting its kinetics. Later Good and Murphy [33] used a mathematical model of hippocampal neuron to show that $\text{A}\beta$ -mediated block of A current could result in increased intracellular Ca^{2+} levels and increased membrane excitability. In their model, they used an immobile Ca^{2+} buffer with a single binding site, a Ca^{2+} extrusion pump (using Michaelis-Menten kinetics), Ca^{2+} diffusion and several VGCCs to regulate intracellular Ca^{2+} levels. They also showed that an increase in Ca^{2+} buffering capacity or decrease in density of VGCCs could reduce the $\text{A}\beta$ -mediated effects causing less increased Ca^{2+} levels and excitability.

In another study, Morse and colleagues [34] used a multi-compartment computational model of hippocampal pyramidal neuron to show that oblique apical dendrites are more vulnerable to $\text{A}\beta$ during back propagating action potential because of their proximity to the axo-somatic region in contrast to apical tuft dendrites and the smaller dendritic diameters. When the excitability of the neuron is enhanced because of the $\text{A}\beta$ -mediated block of A-type K^+ channels, the less attenuated back propagating action potential in oblique dendrites may activate larger number of VGCCs. The resulted larger influx of Ca^{2+} into the cytosol can produce much larger concentrations of intracellular Ca^{2+} due to the larger surface-to-volume ration in oblique dendrites [34].

In contrast to these relatively simple biophysical models, It was only recently that somewhat detailed computer model of a motor neuron linking electrical activity with ATP pathways was constructed by Le Masson and colleagues in a model of amyotrophic lateral sclerosis (ALS) [35]. The model included the plasma membrane Na^+/K^+ ATPases, PMCA, SERCA, plasma and mitochondrial NCX, MCU and mitochondrial dynamics for converting ADP into ATP to meet the cell's energy demands. The multi-compartmental neuron model was based on detailed reconstruction of a cat motor neuron, to which a 100 mm unmyelinated axon was added and included I_h , Na^+ , K^+ , VGCCs and K_{Ca} channels. Using this model, the authors found that a reduction in ATP availability can place motor neurons in a physiological state that leads to prolonged depolarization, massive influx of Ca^{2+} , which ultimately may cause cell death. The authors showed that this process involved a positive feedback loop in which small deficits in available ATP lead to small ion imbalances that, in turn, caused a higher energy demand on the neuron, which led to worse imbalances. The energy deficit could be localized to the axon terminal and still lead to lethal cascade through a retrograde spread that ultimately reached the entire cell. The study provided theoretical evidences that bioenergetics could be a critical determinant of motor neuron differential susceptibility in ALS. They inferred from their findings that a therapeutic strategy aimed at supporting bioenergetics might enhance the capacity of motor neurons to withstand pathological insults, thereby prolonging the lifespan of ALS patients.

Mitochondrial dysfunction plays a central role in almost all neurodegenerative diseases. One of the mechanisms involved in this dysfunction is MAM, which primarily facilitates ER-mitochondria cross talk. It is known that aggregated proteins such as $\text{A}\beta$ and α -synuclein alter the dynamics of MAMs, therefore including MAM dynamics in the computational model of diseases will improve understanding of the emergent behavior of the interactions of several dysfunctional Ca^{2+} regulatory mechanisms. Szopa and colleagues developed a model of ER-mitochondria cross talk to investigate its effects on Ca^{2+} oscillations [36]. This model was extended from an existing model [37] to capture Ca^{2+} regulation by ER, mitochondria and the interaction between ER and mitochondria. The Ca^{2+} influx into mitochondria was modeled via mitochondrial Ca^{2+} uniporters (MCU) located in MAMs sensing elevated Ca^{2+} concentrations in ER and Ca^{2+} uniporter located outside MAMs sensing cytosolic Ca^{2+} levels. The Ca^{2+} release from mitochondria into cytosol was represented by $\text{Na}^+/\text{Ca}^{2+}$ and $\text{H}^+/\text{Ca}^{2+}$ exchangers with the rate of Ca^{2+} efflux regulated by the cytosolic Ca^{2+} concentrations. The Ca^{2+} influx into ER was modeled using a SERCA pump whereas the Ca^{2+} release into the cytosol from ER was modeled using a Ca^{2+} leak channel and $\text{IP}_3\text{Rs}/\text{RyRs}$. A single Ca^{2+} binding protein was included in the model to bind free cytosolic Ca^{2+} . The model produced Ca^{2+} oscillations where the period of oscillations depended on the Ca^{2+} permeability through MAMs. The model predicted that for sufficiently large Ca^{2+} permeability the oscillations disappeared, resulting into high Ca^{2+} levels in mitochondria, which could trigger the early steps of an apoptotic pathway.

Applications to drug discovery

The computational models of neurodegenerative diseases described in the previous section have been helpful in providing mechanistic explanation of neuronal malfunctioning in disease states. Similarly, these models could be used to identify the drugs and their targets

for reducing degeneration or rescuing neuronal functioning. For example, let us consider a computer model of Alzheimer disease in which the effect of A β -induced block of K⁺ channels is simulated by reducing K⁺ channel density. Here, elevation in Ca²⁺ levels is caused by neuronal hyperexcitability. We can use such a model to identify target ion channels (e.g. VGCC), which can be blocked using specific drugs to rescue the excitability of the affected neuron back to the normal range to prevent Ca²⁺ buildup and allow downstream signaling pathways to function properly. Using the dose-response curve for a potential drug and its specificity in blocking a particular ion channel, we can incorporate dose-dependent modulation effects on ion channels into the model and suggest potential treatments. However, we must be aware that our models will only show how to prevent abnormal neuron firing but not take account of how homeostatic regulatory mechanisms, not included in the model, will respond to the intervention. This is a major concern because of the many Ca²⁺-dependent signaling pathways that control transcription and translation. Including accurate details of these multiple levels of homeostatic regulation in computer models is a great challenge for which we don't yet have adequate data or adequate models.

Using computer models to be able to identify drugs for prevention of degenerative disease would require including not only homeostatic mechanisms but also another level of pathophysiological detail. For example, a minimal model would need to implement the dynamics of A β production, aggregation, degradation, and its complete interaction with intracellular and extracellular organelles. This would allow us to intervene in the buildup of A β plaques by reducing A β production from APP using "secretase inhibitors" e.g. LY-450139, a gamma-secretase inhibitor, while rescuing the neuronal function and preventing cell death. Other strategies, like inhibiting A β aggregation into oligomers by using PBT2, or enhancing removal of A β using active vaccines (which produces antibodies to attack A β) could be tested using such multiscale computer models of Alzheimer.

Constructing computer models of neurodegenerative diseases with detailed Ca²⁺ dynamics is necessary to link disease dynamics across multiple scales i.e. disease onset, progression, excitability, plasticity, homeostasis and cell death. Such models will not only allow therapeutic intervention at multiple levels, it will also allow to evaluate the effects of treatment across multiple scales and may provide hints on potential side effects. Detailed Ca²⁺ dynamics are needed because neurodegenerative diseases target multiple Ca²⁺ regulatory processes. For example, in Huntington, Ca²⁺ homeostatic regulation is disrupted via mitochondrial and ER malfunctioning, which is caused by enhanced sensitization of IP₃Rs and RyRs. If we construct a computer model of Huntington with detailed Ca²⁺ dynamics including detailed ER structure, ER regulatory channels and pumps, mitochondrial machinery, Ca²⁺ buffers and plasma membrane pumps and exchangers, we could identify multiple strategies to control enhanced Ca²⁺ release into cytosol. For example, treatments could involve partially blocking VGCCs, IP₃Rs, RyRs, pumps and exchangers, or controlling cytosolic Ca²⁺ with buffers. Any such strategy would be expected to prevent Ca²⁺ dysregulation from damaging downstream signaling pathways whose regulation is essential for the proper functioning of neurons and neuronal networks. These techniques could then be used to identify drugs and to provide guidelines for temporal sequences of drug administration. In the case of Huntington, an actual cure the disease would require intervention at genetic level. In other polygenic diseases, the set of genes might not be

intrinsically pathological but would be adequately controlled by medications, as in the case of type 2 diabetes mellitus.

Conclusions

Computational models of neurodegenerative diseases with relatively simple Ca^{2+} dynamics have been helpful in identifying some processes underlying disease propagation, Ca^{2+} dysregulation and synaptic malfunctioning. However, these models must capture more of the detailed dynamics of molecular pathways responsible for the maintenance of neuronal function in order to be of direct use for translational medicine. In particular, current models are limited due to their inability to capture homeostatic mechanisms and the compensatory nature of multiple pathways, which adjust their dynamics in response to pathology. Future models of neurodegenerative disorders will incorporate detailed Ca^{2+} dynamics along with the causal disease factors, and downstream compensatory signaling pathways that work together to produce cognitive effects and motor control.

Acknowledgments

HA was supported by NIH grant MH060605.

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