HHS Public Access

Author manuscript

Conf Proc IEEE Eng Med Biol Soc. Author manuscript; available in PMC 2020 February 24.

Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2019 July ; 2019: 1956–1959. doi:10.1109/EMBC.2019.8857871.

Pathogenic Processes Underlying Alzheimer's Disease: Modeling the Effects of Amyloid Beta on Synaptic Transmission

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Abstract

The molecular mechanisms underlying Alzheimer's disease (AD) have been and are still under heavy scrutiny to better understand what leads to the onset and progression of the disease, and to design and develop efficacious therapeutic strategies. These decade-long studies have taught us a lot regarding the various molecular pathways involved in the pathology, but a complete dynamic picture of the underlying pathological mechanisms is still missing.

We propose to provide a technological answer to fill this gap by developing and using a computational approach that integrates AD-related experimental findings and their effects on multiple aspects of neuronal function. The present study focuses on implementing one known pathogenic process: the binding of amyloid beta, the hallmark of AD, on NMDA receptors, receptors present in the main type of excitatory synapses in the brain, thereby affecting synaptic transmission and downstream pathways. We describe model implementation and calibration; we then quantify the downstream effects of this disruption both in terms of electrical activity (changes in short-term spiking activity of the postsynaptic neuron), and biochemical pathways activation through changes in calcium dynamics (an important trigger to longer-term changes). The computational approach outlined constitutes an insightful instrument to examine the downstream consequences of multiple pathogenic dysfunctions on higher level observables and sets the path for in-silico discovery and testing of therapeutic agents.

Keywords

Alzheimer's disease; Amyloid and Calcium hypothesis; Synaptic function and dysfunctions; Multiscale computational model of the nervous system; In-silico tool for target identification and therapeutics discovery and development

I. Introduction

Alzheimer's disease (AD) is an irreversible and progressive brain disorder that slowly extinguishes memory and thinking skills, eventually leading to the inability to carry out even the simplest of tasks. Although discovered over a century ago (1906) and despite

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tremendous research efforts, no cure has yet been found, and AD still constitutes the most common cause of dementia among older adults, affecting millions of individuals.

Experimental evidence suggests that damage to the brain likely starts a decade or more before cognitive problems start appearing. During this symptom-free stage, abnonnal deposits of protein result in amyloid plaques and tau tangles throughout the brain. Formerly healthy neurons stop functioning, lose connections with other neurons and die. AD is likely to be caused by copathogenic interactions among multiple factors, including amyloid protein precursor (APP)/Amyloid beta (Ab), the apoE4 allele, tau, a-synuclein, TDP-43, aging, and various comorbidities [1]. How exactly they conspire to impair neuronal functions and survival remains to be determined. Information obtained from quantitative dynamical computational models will undoubtedly shed much needed light on the role of these factors, independently and in combination.

Initially postulated in 1991, the amyloid hypothesis states that extracellular amyloid beta (Ab) deposits are the fundamental cause of the disease. Experimental results suggest that an excess buildup of Ab interferes with NMDA receptor (NMDAR) function, resulting in toxic accumulation of intracellular calcium ultimately leading to neuronal death [2]. Much of the consensus is that Ab interferes with the NR2A and NR2B subunits of the receptor and appears to act as a non-desensitizing agonist, inducing prolonged calcium influx into the neurons. Here we propose to model the effect of this binding and the resulting consequences on synaptic dynamics and downstream events. We specifically focus our attention on an important cellular signaling hub: calcium concentration dynamics in the spine. We briefly describe the overall methodology, model elaboration and calibration. We then discuss our results and outline the applications of this methodology to support a more quantitative understanding of nervous system function and pathological dysfunctions, but also as a tool to support target identification and predict therapeutic efficacy.

II. METHODS

A. Computational Methodology

All models are represented in the systems biology markup language SBML [3], an XML-based representation used for specifying computational models of biological processes that is open and widely adopted (supported by over 290 software tools). The SBML simulation library used is a high-performance and flexible simulation and analysis engine available online (LibRoadrunner v1.5) with Python API [4].

B. NMDA receptor model

We implemented two NMDA receptor models, one expressing the NR2A subunit, and the other expressing the NR2B subunit as proposed by Erreger [5] (Fig. 2a.). The main functional differences between the two subtypes are that the NR2A-NMDA has significantly faster kinetics (for both receptor channel opening and closing) and stronger response than the NR2B-containing receptor. We verified our NR2A-NMDA and NR2B-NMDA model implementations and recorded the functional differences between the two simulated variants using different stimulation pulses of glutamate. Our simulation results (one example of

simulation result is provided in Fig. 3) were validated with respect to the experimental results reported in [5].

C. Incorporating the effects of amyloid beta

Amyloid beta oligomers have been reported to interfere with normal synaptic transmission and activate NMDA receptors even in the absence of glutamate. They act as a non-desensitizing agonist, i.e. they bind to NMDAR and trigger the receptor-associated pore to open in a non-desensitizing manner, leading to abnormally high influx of calcium inside the neuron, which causes calcium overload and neuronal death [6], [7]. To replicate these experimental findings in our in-silico model, we modified the structure of our receptor models and considered Ab as a competitive agonist to glutamate (Fig. 2b. and 2c). Notably, binding of Ab does not induce the receptor to enter in desensitized states. Consequently, the desensitized states D1 and D2 have been removed from the kinetic scheme when Ab is bound. Additionally, Ab has been reported to have a more prevalent effect on NR2A-NMDA then on NR2B [2]. We modified the models in accordance with these findings to replicate experimental observations. More specifically, we constrained the parameters focusing on the effects of Ab on the currents experimentally measured for the different subunits reported in [2], Fig 1.C and 2.B.

D. Calcium concentration model

Postsynaptic calcium concentration is a complex integration of number of processes that influence calcium influx, buffering and efflux of calcium. In addition to NMDA receptors, our model comprises the following elements: voltage-dependent calcium channels R and T types, localized and diffuse calcium buffering mechanisms (smooth endoplasmic reticulum, calcineurin and calmodulin), plasma-membrane calcium pumps, sodium-calcium exchanger and diffusion toward the dendrite (through the synaptic neck). Further details on these models and their associated parameter values may be found in [8] and will be made available on ModelDB [9]. Notably, the postsynaptic membrane is considered not to contain metabotropic receptor. Consequently, calcium influx is taking place through the NMDA-R associated channel only.

E. Model Dissemination

Upon publication, the models presented and their associated parameter values will be made available to the community and shared via the ModelDB website [9].

III. RESULTS

For all simulations, magnesium concentration is maintained at zero; postsynaptic voltage is also held constant at a value of −80mV. For all protocols, we stimulate the presynaptic terminal using a train of presynaptic pulses that leads to releases of vesicles containing glutamate (with 3000 glutamate molecules per vesicle). After diffusion in the synaptic cleft, glutamate binds to postsynaptic receptors (AMPAR and NMDAR), leading to opening of the receptor-associated channel and resulting in excitatory postsynaptic currents. To focus on NMDAR-related currents, the conductance of AMPA receptors is held constant at 0pS.

A. Abnormal influx through NMDA-R associated channel

Average spiking frequencies of a hippocampal pyramidal neuron fall within the range 0.05-5Hz. We therefore simulate in this physiological range at a 2Hz random interval train stimulation to the presynaptic terminal and quantify the response obtained in the presence and absence of amyloid beta. While this train of pulses is applied, we also simulate application of 1mM amyloid beta for 1 second (Fig. 4). We record the current elicited by NR2A-associated channel in response to glutamate only (i.e. insensitive to Ab) (blue trace). We then add the recorded current going through the NR2B-associated channel that is sensitive to Ab only (corresponding to the kinetic schema in Fig. 2b.) (red trace). Finally, we record the currents going through both NR2A-and NR2B-associated channels when both are capable of binding to both glutamate and Ab (corresponding to kinetic schema Fig.2c.). Our results indicate that when the receptors respond to both glutamate and Ab, the presence of amyloid beta leads to a strong and constant influx of calcium through both subtypes. Notably, this influx persists when there is no glutamate to bind to the receptor (i.e. in between the pulses) as long as Ab is applied. This has two direct implications: (i) although the maximum amplitude of the current with Ab is not as high as the maximum amplitude obtained in response to glutamate, the total charge transferred (i.e. the total current integrated over time) is far greater in the presence of Ab; (ii) if we consider the receptor response to a release event the ‘signal’ and its response to no-pulse as the noise, the signal-to-noise ratio decreases dramatically in the presence of Ab, which will undoubtedly alter the downstream transmission of information to the postsynaptic neuron.

B. Changes in calcium dynamics

To further determine the impact of amyloid beta on downstream signaling pathways, we propose to quantify its effects on calcium concentration profile in the spine. To do so, we include in our postsynaptic spine model the elements described in section (II.D.) and record the concentration profile within the spine model in response to the application of 1mM Ab for 1 second. This time, we apply a 5Hz fixed interval train stimulation and record the same elements as mentioned above, focusing now on resulting postsynaptic calcium concentration rather than current. The results are presented in Fig. 5. Several points can be made:

- **i.** Presence of Ab leads to a significant increase in calcium concentration in the spine (reaching almost 3microM for both the red and green profiles).
- **ii.** Stimulation at a higher frequency puts an emphasis on the desensitization that takes place in the receptor as a response to successive glutamate stimulations. This is highly visible on both NR2A and NR2B-containing receptors in the absence of Ab (between 0 and 1000ms).
- **iii.** The green profile has a slower onset than the red profile, i.e. the NR2A receptor that binds only Ab (in the red trace) has a very fast response to application of Ab, while the response of the receptors that bind both glutamate and Ab (green trace) is slower. This is due to the receptor slowly exiting its desensitization states while it binds comparatively more and more Ab (Fig. 2c.).

iv. Once Ab is removed, desensitization of the receptors that bind both glutamate and Ab resumes: the maximum calcium concentration in response to presynaptic stimulation decreases between 3000ms and 5000ms.

v. Notably, there is no desensitization of receptors that bind Ab only (red trace) during application of Ab, which is consistent with our model structure and experimental observations.

IV. CONCLUSION

The work presented here describes a computational model that explores for the first time and replicates the disturbances caused by amyloid beta oligomers observed experimentally on the NR2A- and NR2B-containing NMDA receptors and the consequences on ionic influx and intracellular calcium concentration. The calcium overload has critical consequences for a number of mechanisms: (i) it activates a number of downstream pathways that directly interfere with long-term potentiation (LTP) and depression (LTD) (i.e. affect learning and memory); (ii) it puts significant stress on mitochondrial function and energy metabolism needed to reestablish ionic balances, leading to energy deficiency and production of damaging reactive oxidative species (ROS).

The work presented here is an important step that enables us to quantitatively examine the many detrimental effects of Ab on neuronal activity and survival. Future directions of this work are four-fold, (i) We will first integrate a model of LTP induction that we have already implemented (based on [10]) and examine the relative short-term effects of Ab on learning and memory. (ii) The activity of pumps and exchangers that attempt to reestablish intracellular ionic balances are highly dependent upon local availability of ATP. We propose to link their activity to ATP usage and quantity the energy burden that Ab poses on neuronal activity. (iii) Mitochondria react strongly to calcium gradients in the cell; we will link a mitochondria model currently being developed (based on [11]) and extend it to study how Ab-related disruptions lead to increased production of reactive oxidative species (ROS), a major source of oxidative stress in the cell [12]. (iv) Finally, we will use the resulting integrated platform to perform a sensitivity analysis and establish a quantitative map of the parameters landscape that pose a potential threat to neuronal viability and identify potential therapeutic targets capable of alleviating these threats and promote cell survival.

Acknowledgments

This work was supported in part by National Institute of Biomedical Imaging and BioEngineering (NIBIB) grant P41 EB001978 and U01 GM104604 and U01 EB025830 from the National Institute of Health.

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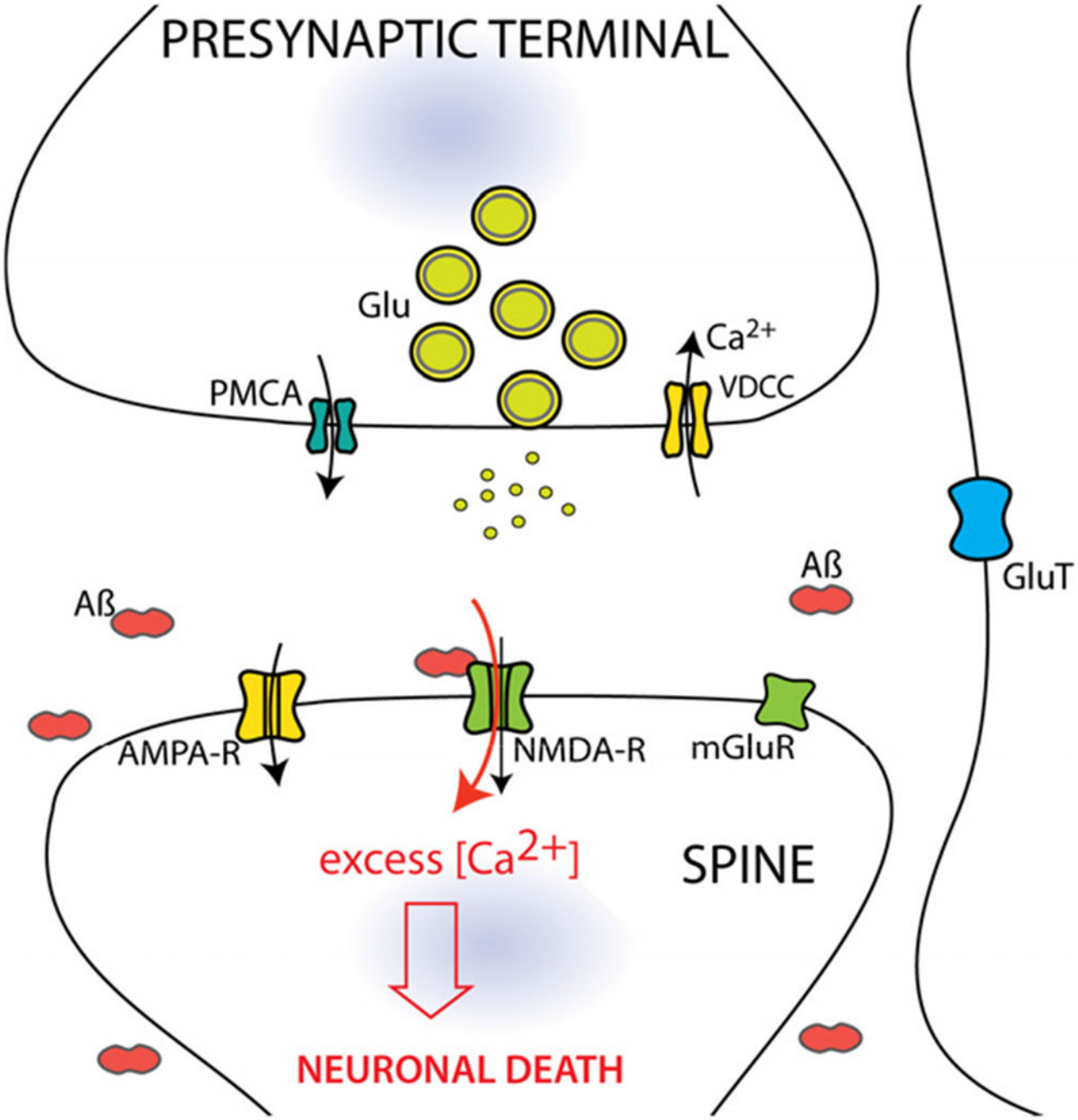

Figure 1.

Amyloid beta oligomers have been reported to interfere with normal synaptic transmission (red arrow): they bind with glutamatergic receptor NMDA-R. The receptor associated channel opens, resulting in a toxic excess influx of calcium inside the cell, ultimately leading to neuronal death.

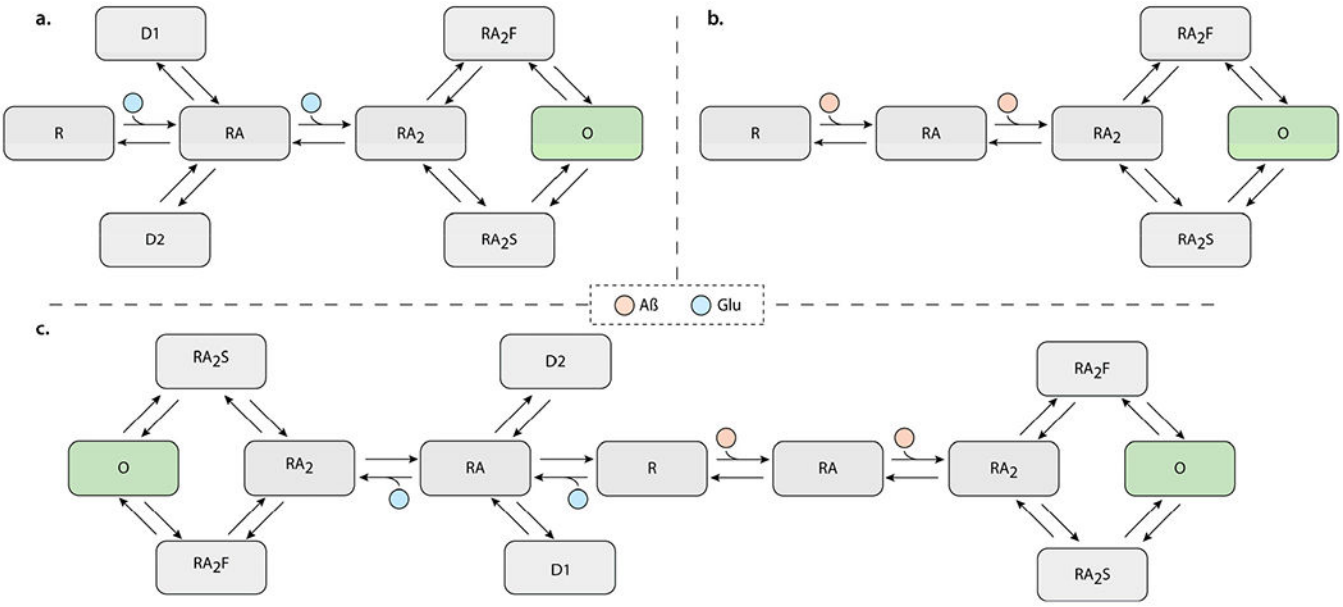

Figure 2.

Kinetic schemes for the NMD A receptor model adapted from Erreger [5]. **a.** Original scheme with two binding sites for the agonist glutamate (blue) that leads to opening of the receptor-associated channel (O state) through fast (RA2F; receptor bound with two agonists) and slow transition states (RA2S). Notably, the model contains two desensitization states (D1 and D2) that can become activate when one glutamate binds to the receptor. **b.** Amyloid beta (red) binds to the same binding sites as glutamate. This binding leads to the receptor opening through similar slow and fast transition states (RA2S and RA2F). Notably, D1 and D2 desensitization states are not present with Ab binding. **c.** Complete kinetic schema with competitive binding of glutamate and amyloid beta.

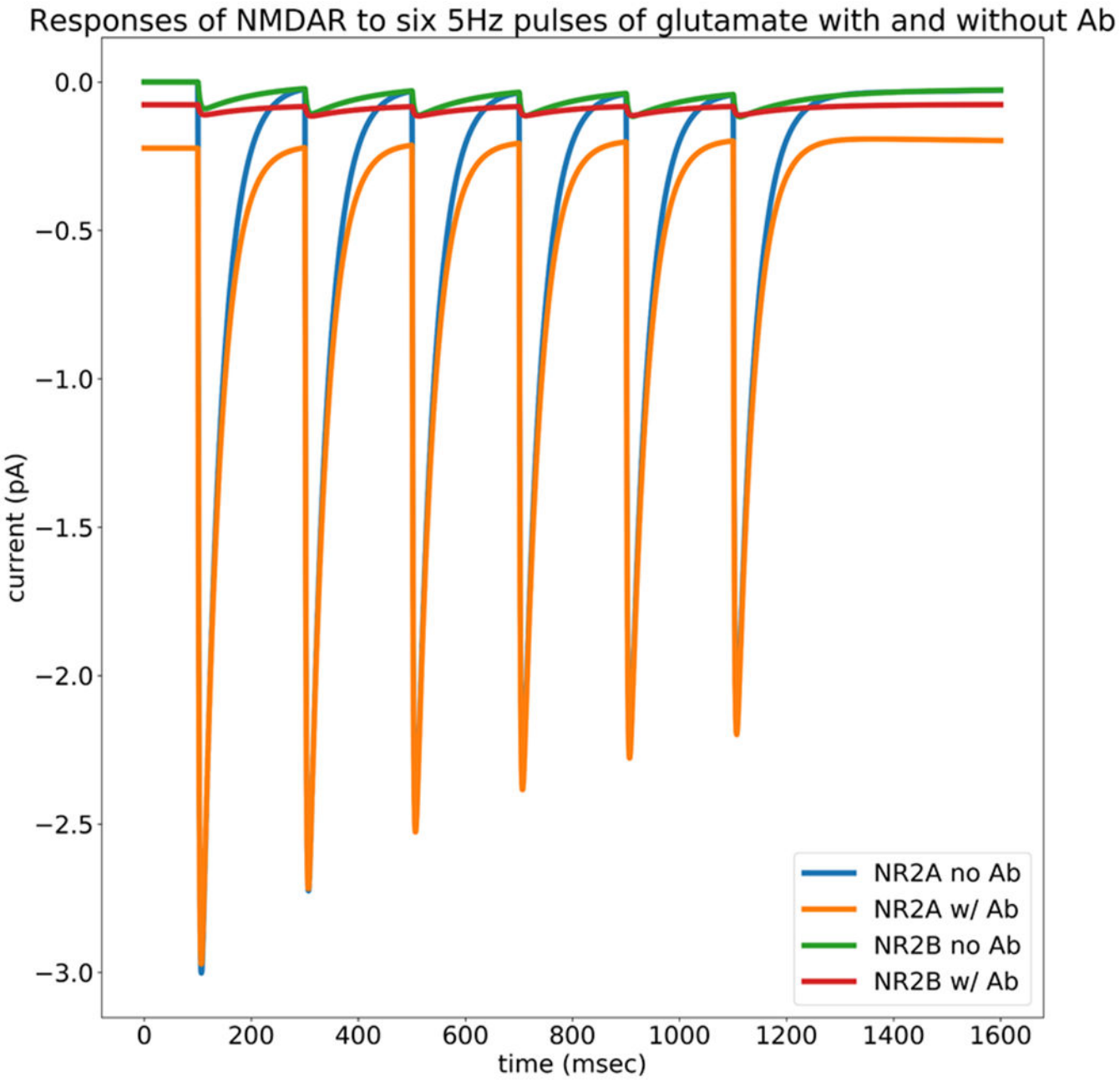

Figure 3.

Response of the NR2A- and NR2B-containing NMDAR models to six 5Hz pulses of glutamate in the presence and absence of 1 μM Ab (bath). Results without Ab may be directly compared to [5] Fig 8A).

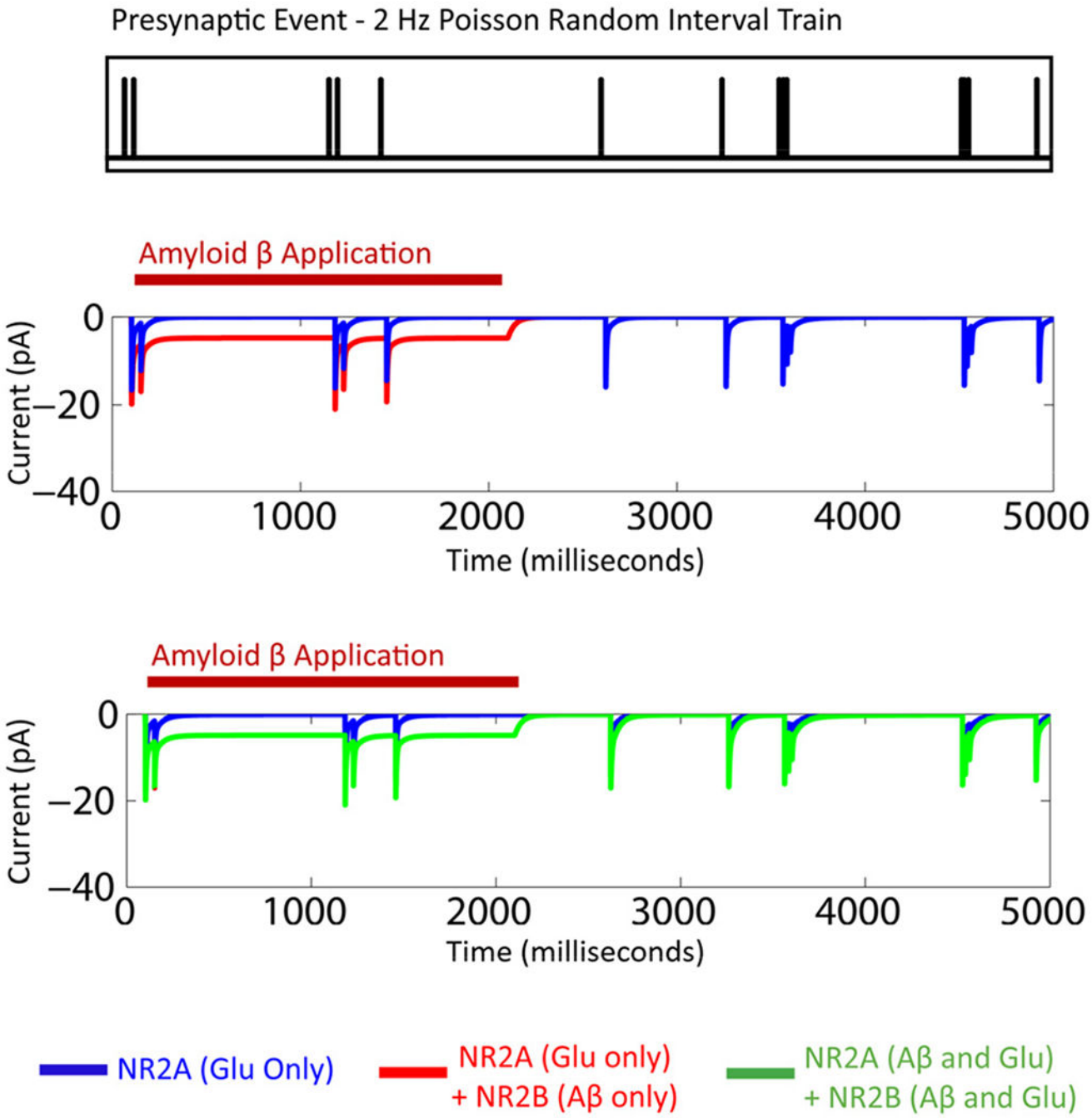

Figure 4.

Response of NMDA receptor containing subtypes NR2A and NR2B to a random interval train of presynaptic release events in the presence and absence of amyloid beta. (Top) Series of simulated release events (2Hz random Poisson distribution); this series of spikes corresponds to events of vesicular release of neurotransmitter which then diffuse in the cleft and bind to the NMDAR binding site. The blue trace corresponds to the NR2A model and it only binds glutamate, and consequently does not respond to the application of amyloid beta. The red trace corresponds to the blue trace added to the response of the NR2B model that

binds Ab only. The green trace corresponds to both NR2A and NR2B models responding to both glutamate and Ab.

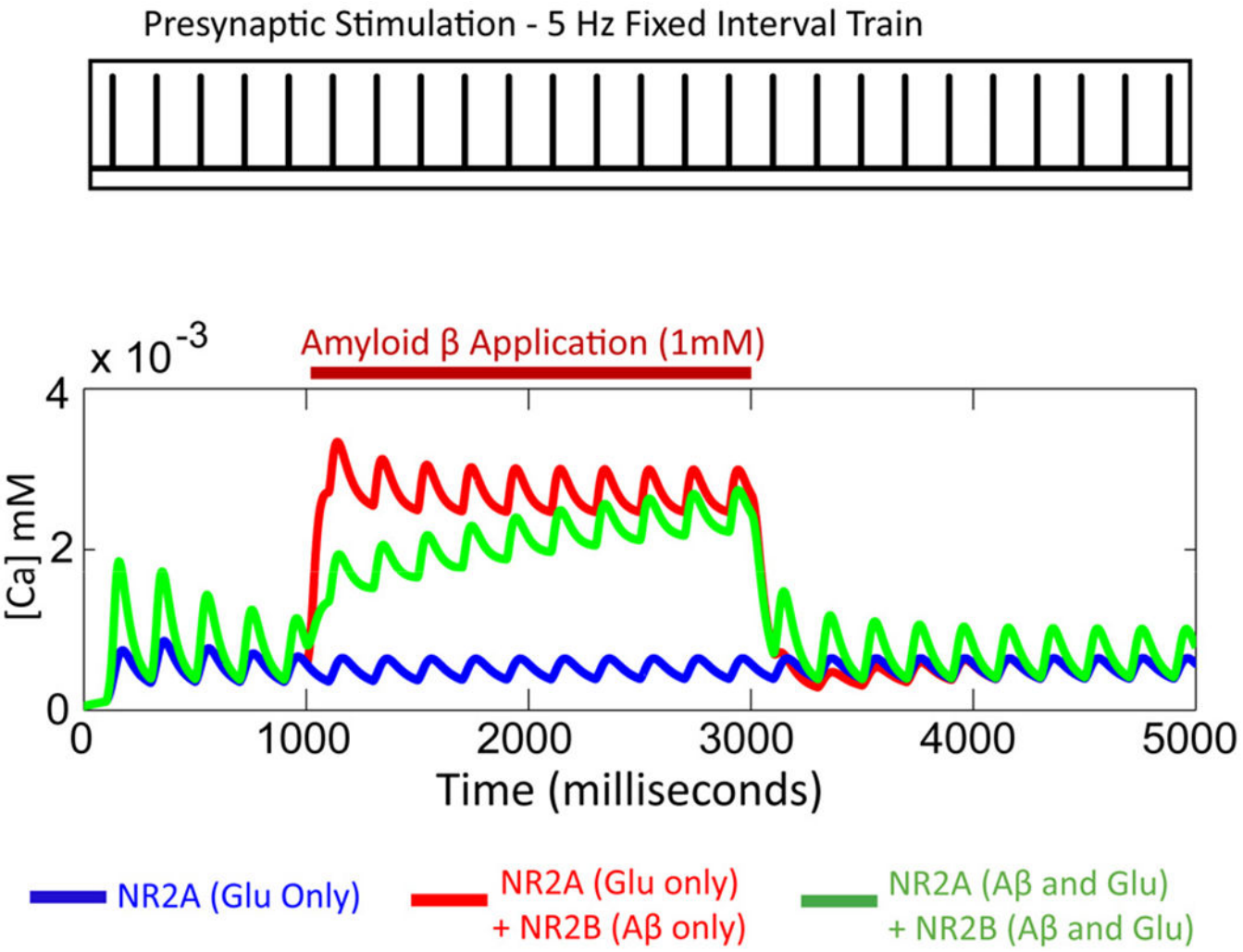

Figure 5.

Response of NMDA receptor containing subtypes NR2A and NR2B to a 5Hz fixed interval train of presynaptic release events in the presence and absence of amyloid beta. (Top) Series of simulated release events (5Hz); these events correspond to vesicular releases of neurotransmitter which then diffuses in the cleft and binds to the NMDAR binding site. Currents through postsynaptic receptors result in an influx of calcium, and calcium concentration in the spine increase. The blue trace corresponds to the increase in postsynaptic calcium concentration due to opening of the NR2A-associated channel when it binds glutamate only. The red trace corresponds to the blue trace to which is added the calcium concentration due to influx through the NR2B model that binds Ab only. The green trace corresponds to calcium profile obtained when both NR2A and NR2B models respond to both glutamate and Ab.