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Computational Investigation of Effects of Spines and AMPA Receptor Desensitization in Temporal Integration in Striatal Medium Spiny Neurons

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Abstract - The reward pathway in the brain is an important circuit for various behavioral and sensory-motor aspects of an organism. The nucleus accumbens (NAcb), which constitutes the major subdivision of the ventral striatum, plays an important role in the reward pathway. It is also considered as the major site of action for many drugs of abuse. Majority of neurons in NAcb are GABAergic Medium Spiny Neurons (MSN). At cellular level any changes in reward related behavior have been attributed to changes in the responses of the MSN. These neurons receive synaptic input over number of spines which are present on complex dendritic arbors. Properties of spines and synapses may cause distortion of the final output at soma and can create specific computational problems in MSN. For example desensitization of AMPA receptor causes paired pulse depression of excitatory post synaptic potential (EPSP) due to which neuron may not be able to estimate accurate incoming synaptic activity. Also, morphological changes in spine can affect synaptic plasticity. In our current work we have attempted to investigate the role of spines in shaping EPSPs through computational simulations using the model of MSN. It was found that, receptor desensitization and high input resistance spines alter the EPSP amplitude and width and hence found to be affecting synaptic integration pattern. Also, the location and clustering of the spines influences the EPSPs.

***Index Terms*—Reward pathway, MSN, spines, AMPA, integration.**

I. Introduction

There are different regions in the brain, which are anatomically as well as functionally different from each other. The specific connectivity of circuits to some degree, set in expected patterns within the brain, lead to the notion that certain places in the brain are specialized for certain functions. One such circuit in mammals which promotes learning processes and activities that are essential to the survival of the individual and the species is the reward circuit. Reward circuit consists of group of neurons, activation of which causes strong feeling of satisfaction and pleasure. The reward circuit is implicated in a number of pathologies and emotional disorders such as drug addiction and schizophrenia [1]. NAcb is an important part of the reward circuit and considered as the 'pleasure center' of the brain. The principal neuronal cell type in the NAcb is the Medium Spiny Neuron (MSN), which is its primary output cell. At the cellular level, reward processing and reward based learning have been attributed to changes in the responses of MSN of the striatum. Physiological parameters of the striatum are believed to get changed because of the emotional disorders [1]. This in turn is believed to affect the input-output relations of MSN in the striatum. MSNs perform a central role in sensorimotor processing by integrating many excitatory inputs located across their dendritic arbor to fire an action potential (AP).

Like many other (approximately 90% of the principal neurons of the brain) neurons, in MSN also, excitatory inputs are formed on synapses present on tiny bulbous protrusions on dendrites, which are called spines [2]. In developing as well as adult brains, spines are shaped depending on animal's experiences [3]. For example, in immature hippocampus, density and morphology of spine is altered during the long-term potentiation (LTP) [4]. LTP is considered as the cellular correlate of the learning and memory spines are considered as storage site of synaptic strength and can be of importance in neural processing [3]. Therefore, spines

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have been attracting a lot of attention from neuroscientists and are being studied intensively for the ways in which their structure and function can impact neurophysiology.

However, the dependence of synaptic responses on the temporal and spatial distribution of synaptic inputs on these spines is not known. It was found that synaptic responses can summate linearly, sublinearly or supralinearly depending on the spatiotemporal pattern of activity [5]. Experiments conducted by Carter et al. (2007) have shown that repetitive activity at single inputs leads to sublinear summation, reflecting AMPA (Alpha-Amino-3-Hydroxy-5-Methyl-4isoxazole Propionic Acid) receptor desensitization. In contrast, asynchronous activity at multiple inputs generates linear summation. Such type of desensitization was observed in downstate as well as up-state of MSN. Synchronous activity at clustered spines also leads to supralinear summation of synaptic responses at depolarized membrane potential.

With their high density, chemical and electrical properties together with desensitization of AMPA receptors (AMPAR), spines can play a critical role in integrative properties of MSN. But spines are extremely small in size, approximately <2 µm in length, with a bulbous, spherical head (0.5-1.5 µm diameter) connected by a narrow neck (<0.5 µm diameter) to the parent dendritic shaft [2] and therefore despite their potential importance in neuronal function, recording electrical signals from them as experimental evidence is difficult. Computational approach will overcome this limitation of size. With the help of computational view, observed phenomenon such as potential at distally located spine head or neck which is not easily accessible experimentally can be understood by simpler way.

II. METHODS

A. Model Building

Our simulations were carried out using a multicompartment stylized model [1] of the MSN with biophysical properties constrained by in-vivo intracellular recordings and was built using the NEURON simulation platform. Four primary dendritic branches were included. Each of these bifurcates to produce secondary dendrites, each of which further bifurcates to give 16 tertiary dendrites. Spines were modelled as having three electrical sections i.e. post synaptic density (PSD), head and neck, which are connected with an axial resistance [6]. Detailed morphology of the model is as shown in Fig.1.Various intrinsic currents in MSN known to be present (14 in number) were distributed in the model. The model included all the current channels found to be present in the actual cell and their conductance values were in accordance with those as stated by Wolf et al. (2005). Synaptic currents were also included in the model as point processes. Excitatory glutamatergic synapses (AMPA and

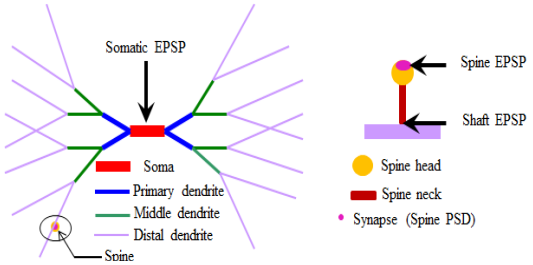

Fig. 1. Detailed morphology of a model cell with placement of spine and recording sites (black arrow).

NMDA (N-Methyl-D-Aspartic Acid) were placed on spine PSD along with calcium channels, other intrinsic currents were included in the spine head and neck and inhibitory GABAergic synapses were also distributed throughout the cell based on available literature. The original model was modified to incorporate AMPAR- mediated EPSP desensitization.

B. Simulations

1) *Single spine stimulation*

To assess the effect of spine on the amplitude and width of EPSP, pilot study was done in which a single spine was placed at the center of the 1st distal dendrite (Fig. 1). A single EPSP is recorded locally at the site of the input i.e. in the spine PSD for spinous input termed as spine EPSP or EPSPspine or at the dendrite for dendritic inputs termed as dendritic EPSP, at soma (somatic EPSP, the EPSP which has propagated from spine to soma) and in case of spinous inputs, in the shaft, at base of the spine, termed as shaft EPSP, where the spine neck is connected to its parent dendrite. Amplitude and half width (HW) of the EPSPs (spine EPSP and dendritic EPSP) were compared by placing the spines at different locations on dendrites. AR is calculated by taking ratio of spine EPSP to the base EPSP (EPSPdend) for different values of R_n. R_n is changed by varying the diameter of the neck.

2) *Multiple spine stimulation*

Each distal dendrite is divided into 11 segments using d_lambda rule of NEURON. To see the interaction between the neighboring spines 11 spines were placed, one each at every compartment on a distal dendrite as shown in Fig.2.Voltage recorded from soma and at the input was compared for spiny and aspiny model for chosen conditions e.g. (1) all the synapses activated synchronously for spinous as well as aspinous dendritic input and (2) Only one synapse is activated at a time (other

10 synapses were silent). To test the effect of spine cluster on EPSP, spines were placed in a cluster at the proximal location (~58 µm from soma) and at the distal location (~380 µm from soma) on distal dendrite (Fig. 3 A and B) and somatic and spine EPSPs were recorded by varying number of spines in cluster.

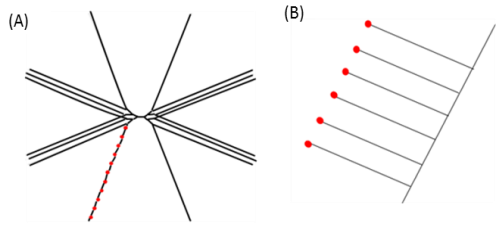

Fig. 2. (A) Placement of spines (Each red dot indicates position of a single spine) (B) Expanded view of circled section in Fig. A.

These results were then compared with the results, when spines were not placed at the same position but spaced at approximately 8 µm from each other with 1st spine being placed at ~58 µm from soma for proximal cluster and ~380 µm from soma for distal cluster.

A cluster of 4 spines was formed at the proximal and distal end of the 1st distal dendrite at positions mentioned above and remaining (7) spines were placed one at each compartment as shown in the Fig. 3 (C and D). Results were then compared with EPSP recorded when spines were distributed uniformly.

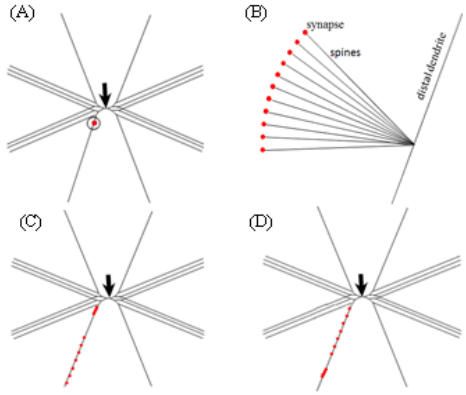

Fig. 3. Position of spine cluster (A) all spines at one position (B) expanded view of circled section of A (C) proximal cluster and (D) distal cluster (black arrow indicates recording site).

3) *Spatio-temporal integration*

To investigate the role of spines in synaptic integration in MSN, simulations were carried out to see the effect of these on temporal integration window. Time period over which AP may be generated as a result of integration of synaptic inputs is termed as temporal integration window. Number of spines was distributed over the dendrites but at the same location as shown in the Fig.4 and this was referred as one group. Two such groups of spines were used, each of which consist of 16 spines, placed at middle (6th compartment) of the distal dendrite. All the spines from each group were activated synchronously at different time intervals and peak depolarization at soma was recorded. In all the conditions the conductance of AMPA and NMDA receptors was tuned to obtain same peak somatic depolarization ~ – 61.4 mV on activation of one group.

The minimum value of conductance which gives this EPSP was chosen in such a way that,

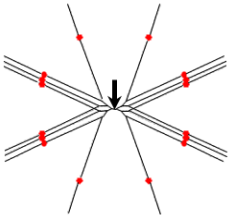

Fig. 4. Placement of spines and recording site (soma, black arrow) for temporal integration protocol (Each red dot represents single spine).

1. EPSP produced was subthreshold when synapse was activated individually (threshold for AP is – 44.6 mV).
2. On summation of two EPSPs at the same time instance, did not produce an AP.

III. RESULTS

Results of computational simulations show that presence of a spine on a dendrite alters the amplitude and width of EPSP and it depends upon the location of the spine. It has been found that in aspiny model activation of a single synapse resulted in a EPSP of 1.11 mV at soma and 14.42 mV at synapse (dendritic EPSP). In contrast, in the presence of a single spine, somatic EPSP reduced to 0.95 mV and spine EPSP was increased to 29.34 mV (Fig.5).

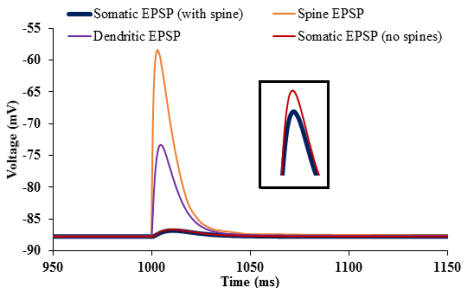

Fig. 5. Effect of the spine on EPSP. Inset shows the difference in somatic EPSP for aspiny and spiny model on extended scale.

As the spine EPSP propagates towards soma, attenuation of ~60% in amplitude was observed at the shaft i.e. base of the spine and ~96% at the soma (Fig.6). Also a spine caused EPSP HW to increase by 7.47% at soma and decrease by 8.33% at synapse (Fig.7).

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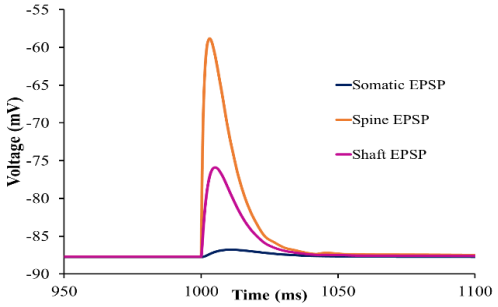

Fig. 6. Attenuation of EPSP at shaft and soma

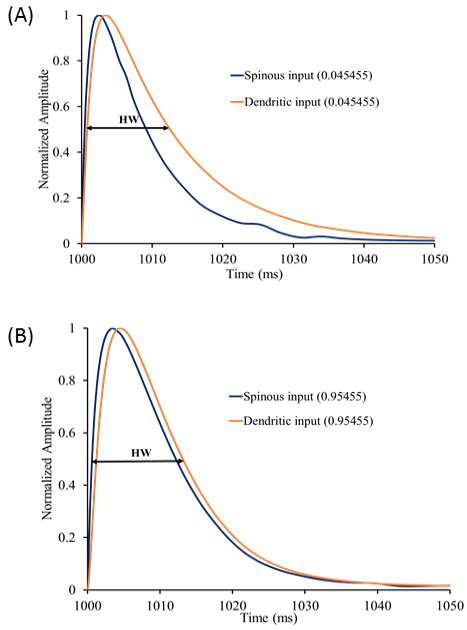

Fig. 7. Normalized amplitudes of spine and dendritic EPSP (figures in the bracket indicate position of the spine (spinous input) or the synapse (dendritic input on the distal dendrite)).

Observed percentage change in amplitude and HW at different locations is given in the Table I. Upward and downward arrow indicates increase and decrease in the percentage respectively.

A. Effect of neck resistance on EPSP

When EPSPs were recorded for different values of spine neck resistance (Rn), it was found that both spine and shaft EPSPs depend on Rn but in opposite ways. Somatic and shaft EPSPs get attenuated whereas spine EPSP get boosted with increasing Rn as shown in the Fig.8. To illustrate this effect, AR was plotted as a function of R_n as shown in the Fig.8, which also increases with increase in R_n. As is evident from the graph of AR vs R_n (Fig. 6.4 C), at R_n = 500 MΩ, AR is ~2.5 (dotted line) This means, spine EPSP is ~2.5 times greater as compared to its shaft EPSP.

These results indicate that voltage measured at the spine is different as compared to that at the dendritic shaft for all the tested values of R_n and hence, to some extent verifies the role of a spine neck in electrical compartmentalization and filtering the potential as they propagate from spine head to soma.

TABLE I. EFFECT OF SPINE ON EPSP AMPLITUDE AND WIDTH

Location		At 0.045		At 0.5		At 0.77		At 0.95	
		At soma	At i/p	At soma	At i/p	At soma	At i/p	At soma	At i/p
Amplitude (%)		18↓	436↑	15.04↓	103.52↑	13.81↓	62.56↑	12.88↓	48.47↑
Half width (%)		10↑	34↓	7.47↑	8.33↓	0.92↑	7.5↓	0.42↑	1.88↓

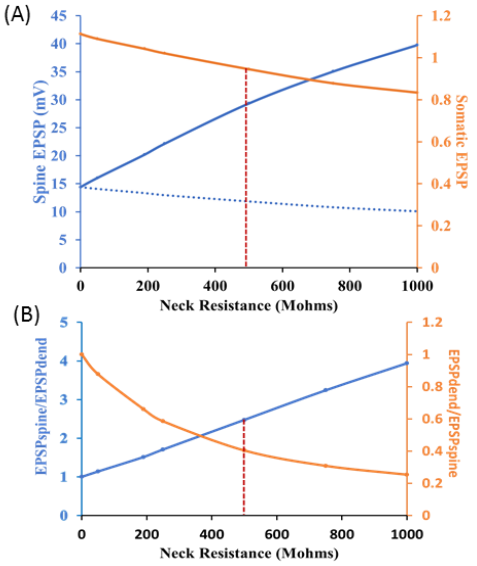

Fig.8. Influence of R_n on EPSPs (A) Spine, Somatic and Shaft EPSP (dotted line) (B) AR as a function of R_n (R_n=500 MΩ at dashed line).

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As can be seen from Table I, there is a significant difference in the amplitude of spine EPSP and dendritic EPSP, but difference in the EPSP HW is not significant. It has been found that farther the spine from the soma, change in the amplitude and HW is lesser. When normalized amplitudes of dendritic and spine EPSPs were compared (Fig. 8), it has been found that spine EPSP rises faster as compared to dendritic EPSP. Also the difference between HWs of both EPSPs is greatest for the spine which was placed at proximal end of the dendrite. When all 11 spines were stimulated synchronously, the EPSP recorded at each synapse (spinous input) for spiny model was greater in amplitude as compared to EPSP for aspiny model (dendritic input), but the somatic potential was lesser for a spiny model as compared to aspiny model. Whereas, on activation of a single spine, EPSP amplitude at that synapse was greater this was placed on activated spine.

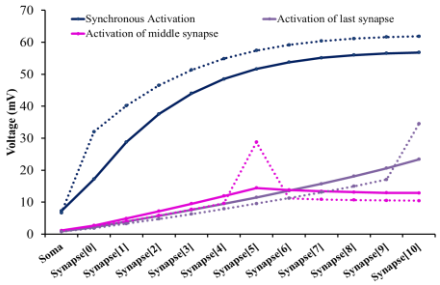


Fig. 9. Stimulation of multiple spines (Solid lines - activation of dendritic input, dotted lines – activation of spinous input).

As is shown in the Fig.9, on activation of 6th spine (middle), EPSP recorded at this synapse was ~twice the respective EPSP for dendritic input but it was lesser at all other locations than the respective EPSPs recorded for aspiny model. Similar results were found when EPSPs were recorded by activation of a single spine at different locations. When simulations were carried by activation of cluster of spines which was formed by placing all the spines at the same position as shown in Fig. 3B, it was found that the somatic potential increased with number of spines in a cluster (Fig.10).

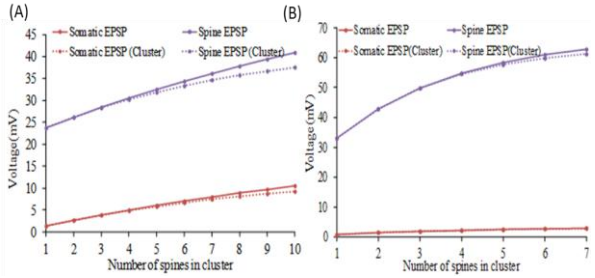
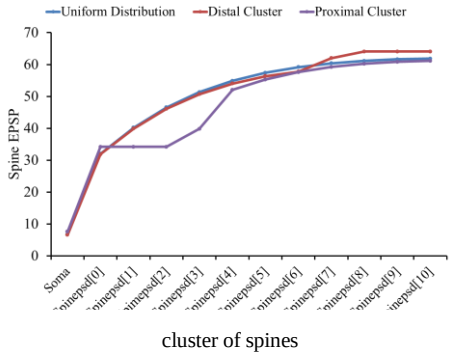


Fig. 10. Stimulation of (A) proximal cluster (B) distal cluster (Solid line – potential recorded by placing the spines at one point, dotted lines – potential recorded by placing the spines closed to each other).

On comparison of these results, with those, when spines were placed closed to each other, it was observed that for lesser number of spines (<5), there is no change in the potential for two conditions. But as shown in the figure the difference in the potential goes on increasing with the number of spines in the cluster, having greater potential when all the spines are placed at the same point. Similarly, when spines in distal cluster were stimulated, it was observed that there is no significant change in the potential in these two conditions as shown in Fig.10 B. When potentials recorded by stimulation of proximal and distal cluster (4 spines) compared with that of uniform distribution, it was found that spine EPSP for uniform distribution is smaller when spines were clustered proximally and larger for distally clustered spines (Fig.11).

Fig.11. Comparison between uniform distribution of spines and



cluster of spines

It is evident from Fig.5, that the amplitude and the width of the synaptic EPSP are affected by presence of spine. All the results of our simulations suggest that, since synapse is the site of integration of inputs, the integration pattern will be affected in spiny model. Simulations were carried to determine temporal integration window and it was compared with that of aspiny model. Figure 12 represents the somatic recording generated for a delay (Δt, t_{S2}-t_{S1}, relative activation time) of 35 ms for spiny (blue trace) and aspiny (pink trace). As it can be seen from the figure that aspiny model is not able to generate an AP whereas, spiny model generated the AP for the same activation delay. Fig. 13 shows the peak somatic depolarization recorded for both the model, as a function of delay, following activation of the two inputs with reference to Action Potential Threshold (APT, dashed line). It is clear from the figure that temporal integration window for spiny model (blue trace, 42 ms) is considerably wider as compared to that (green trace, 28 ms) of original model.

When simulations were carried out with aspiny model in presence of AMPAR desensitization (orange trace), it was found that temporal integration window was ~33% narrower as compared to original model (Fig.13).

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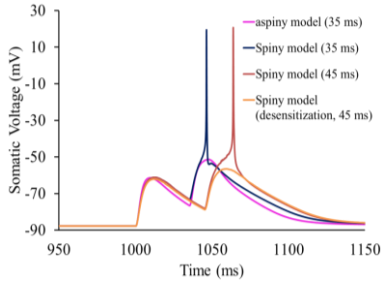

Fig.12. Summation of EPSPs at soma at different activation times

It was observed that even for a delay of 45 ms, spiny model could generate an AP (brown trace, Fig.12) but in presence of AMPAR desensitization, it failed to produce an AP (Orange trace). Simulation of spiny model (maroon trace, Fig.12) resulted in ~17% narrower temporal integration window due to receptor desensitization. This stems from the fact that AMPAR desensitization leads to postsynaptic depression of the EPSP generated by paired stimulus. Due to the decreased amplitude of the second EPSP which is generated at different delays, time window during which two inputs can integrate and attain APT decreases.

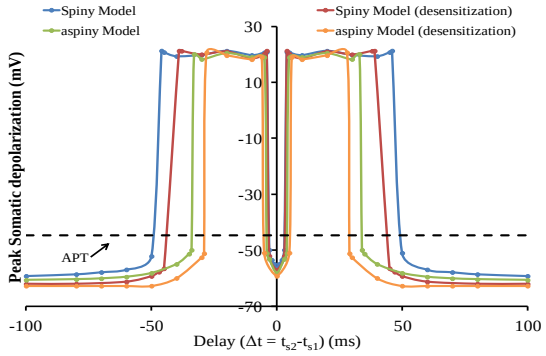

Fig.13. Effect of spine and AMPAR desensitization on temporal integration window (dashed line represents action potential threshold).

Values of temporal integration window for all the four models are given in Table II.

TABLE II. TEMPORAL INTEGRATION WINDOW

Model type	Temporal Integration Window (ms)
aspiny	28
aspiny (with desensitization)	22
Spiny	42
Spiny (with desensitization)	35

IV. CONCLUSIONS

It has been reported previously by several authors [2], [7], [8], [9], [10] that dendritic spines act as filters and are responsible for attenuation of EPSPs at soma. Results of our investigation show that dendritic spine affects the amplitude and half width of EPSP. Stimulation of a single spine showed that amplitude of EPSP at spine PSD is different than that of its parent dendrite. It has been found that amplitude of EPSP is affected not only due to presence of spines but its location, cluster of spines and even the location of cluster. For the spiny model the window over which AP is elicited is wider as compared to aspiny model whereas AMPAR desensitization constrains the temporal integration window. Therefore, spines along with receptor desensitization could offer a means of altering MSN excitability. Wider integration window in presence of spine may drive the MSN to fire in temporal integration mode while, in presence of AMPAR desensitization narrower temporal window for spiny model may change the mode of integration to coincidence detection [11].

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