The effect of NMDA receptors on gain modulation in cerebellar granule cells

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Abstract

The bandwidth for divisive gain modulation by shunting inhibition in cerebellar granule cells is restricted by NMDA-receptor mediated currents. The amount of modulation of high frequency mossy fiber rates is significantly reduced. This effect is mainly caused by the increased current flow into the cell, and not due to a reduced variability in the input current

Keywords: gain modulation, granule cell, NMDA, cerebellum

1. Introduction

Gain modulation is a powerful computational mechanism by which the way neurons combine and process information can be regulated. It has been proposed to be involved in sensory processing, attention modulation and the computation of coordinate transformations [11].It comprises the modulation of the response of a neuron to its input by a gain control parameter. In a rate-based scheme of information transmission the response (gain) of a neuron is defined as its mean firing rate.
Gain modulation usually consists of an additive and a multiplicative component (sometimes called subtractive and divisive gain when the direction is opposite). Additive gain modulation denotes a mere translation (offset) of the input-output relationship of a neuron and is for example computationally useful to subtract baseline excitatory activity. Multiplicative gain modulation alters a neuron's sensitivity to input rate changes (it changes the slope of the input-output curve) and extends the computational possibilities considerably [11].
Gain modulation has been investigated for cells with numerous (small amplitude) synaptic inputs like e.g. cortical pyramidal cells with excitation and inhibition in approximate balance. It was found that the neuronal response to an excitatory drive could be modulated by the overall level of background synaptic input [3].
It has been shown that also in cells with only a few (large amplitude) excitatory synaptic inputs – cerebellar granule cells – gain modulation is possible.In this case the level of shunting inhibition acts as the gain control parameter [8].
An example of a system displaying almost pure additive gain is a cell driven by tonic excitatory current injection with as gain control parameter the level of shunting inhibition. Although the subthreshold membrane voltage – current relationship suggests multiplicative scaling, it was shown that the input-output curve merely shifts

[5]. In the above mentioned case of balanced excitation and inhibition it is possible to attain approximately pure multiplicative gain. In the case of gain modulation by shunting inhibition (in the granule cell), multiplicative gain is always accompanied by additive gain. Additive gain is caused by a change of the membrane conductance. Multiplicative gain has been shown to depend upon the amount of variability of the membrane potential of a cell .
In the granule cell study [8] the synaptic input to the neuron is simulated using a dynamic clamp approach. High variability of the membrane potential relied on the stochastic timing of input events in addition to the fact that only high-amplitude EPSCs with fast kinetics, corresponding to the AMPA component of synaptic transmission, were included. Granule cells contain also NMDA receptors and although they contribute only a small percentage to the peak EPSP amplitude, they carry due to their much slower kinetics a similar amount of charge during a single EPSC as the AMPA receptors. In this study we investigated the influence of this NMDA current on the input-output relationship of granule cells.

2. The Model

A conductance-based model of the granule cell (based upon [7]) was constructed. The cell consists of one compartment with a diameter of 10 μm and a specific membrane capacitance of 1 $\mu F/cm^2$. The model contains 6 types of active membrane channels: a fast Na^+ channel, a delayed rectifier K^+ channel, an A-type K^+ channel, a high-voltage activated Ca^{2+} channel, a Ca^{2+} activated K^+ channel and an anomalous inward rectifier Na^+/K^+ channel.
The value of the threshold for AP generation has an important role in the amount of NMDA-receptor mediated current, because of the strong voltage-dependence of the Mg^{2+}-block of the NMDA receptors. Various values have been reported for the threshold, from -49 mV [8] to -35 mV [1,2]. In the model the threshold has been set to -41.3 mV. Tests were done with a threshold +5 mV and -5 mV. No significant changes were found in the former case, while in the latter case the NMDA current components were strongly reduced. The resting membrane potential in our model is -62.9 mV, giving a comparable voltage difference between threshold and resting membrane potential as has been reported [1].
Granule cells receive excitatory input from on average 4 mossy fibers. This was modelled by 4 synapses, containing each an AMPA and a NMDA conductance, which were stimulated with independent Poisson spike trains of various mean frequencies. The kinetics of the AMPA receptors are described by a rise time constant of 0.13 ms and three decay time constants of 0.42 ms, 2.71 ms, 15.5 ms, contributing respectively 60 %, 29 %, 11 % to the peak conductance [8]. Because of the fast kinetics saturation of the receptors is negligible and therefore not taken into account.
Granule cells have both synaptic and extrasynaptic NMDA receptors. A single release event activates predominantly (77 %) the synaptic receptors. The kinetics after a single release event consist of a 10-90 % rise time of ± 5 ms and decay time constants of 15 (55 %) ms and 93.1 ms (45 %) [10]. The behaviour after multiple release events within a short time is less well-known. The relative synaptic and extrasynaptic contributions to the current might change, resulting in different overall kinetics. Moreover, because of the much slower kinetics than in the AMPA case possible saturation of NMDA receptors must be taken into account. However it is unknown

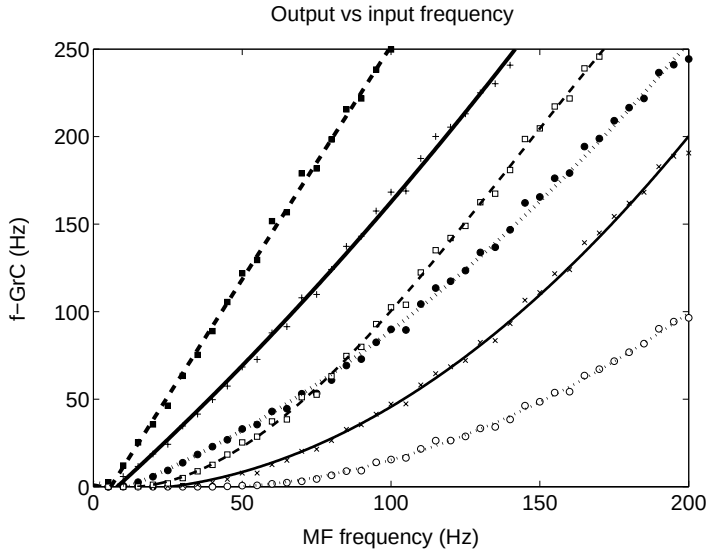

Figure 1 ff-curve for 3 configurations:
1. Without NMDA: filled (0 nS) and empty (1 nS) circles
2. With NMDA (64%): plusses (0 nS) and crosses (1 nS)
3. With NMDA (128 %):

how fast saturation occurs for synaptic and extrasynaptic receptors in cerebellar granule cells. There is evidence that synaptic NMDA receptor are not saturated by a single release event and in a particular case [12] the saturation level after a single event was estimated to be 31 %. We take here the approach to model the NMDA conductance by the kinetics given above and saturating at 3.3 times the peak conductance (after a single event), thereby largely neglecting the effects of extrasynaptic NMDA receptors.
The saturating NMDA conductance was modeled using the equations [4]:

$dg_{NMDAf,s}(t)/dt = T_{f,s}(t)(1- g_{NMDAf,s}(t))- g_{NMDAf,s}(t)/\tau_{decayf,s}$

$dT_{f,s}(t)/dt = - T_{f,s}(t)/\tau_{f,s}$

$g_{NMDA}(t) = g_{NMDA,peak}\,(0.55\, g_{NMDAf}(t)+0.45\, g_{NMDAs}(t))\, Mg(V(t))$

where $T_{f,s}(t)$ is increased after each incoming event with a value $T_{peak,f,s}$
and the the voltage-dependent Mg^{2+}-block is described by:
$Mg(V(t)) = 1/(1+\eta\,[Mg^{2+}]\, e^{-\gamma V(t)})$. The used constants were: $\tau_f = 2$ ms, $\tau_{decay,f} = 5.5$ ms, $T_{peak,f} = 0.26$ ms, $\tau_s = 5.5$ ms $\tau_{decay,s} = 93.1$ ms, $T_{peak,f,s} = 0.08$, $\eta = 0.28$ mM^{-1}, $\gamma = 0.062$ mV^{-1}, $[Mg^{2+}] = 1.2$ mM)
The ratio between the peak of a single EPSP and the potential difference between threshold and resting membrane potential is in the granule cell approximately 0.5 [1]. The AMPA and NMDA peak conductances were tuned to match this value, resulting in peak EPSPs of 11-13 mV. A ratio of NMDA versus AMPA peak conducance of 0.64 has been reported [10]. It was also found that NMDA receptors accounted for 30% of the peak amplitude of the EPSP after a single stimulation [1]. In our model this required a NMDA to AMPA peak conductance ratio of 1.28, similar to the value found in the cortex [9]). We investigated both these cases.

3 Results

Mossy fibers can fire at high rates, up until 300 Hz [6]. We investigated the (mean) granule cell firing rate as a function of an average firing rate of 4 afferent mossy fibers between 0 and 200 Hz. Three different configurations were tested both in the presence and the absence of 1 nS shunting inhibition (see figure 1): one without NMDA receptors (N0) and two with NMDA receptors, with NMDA peak

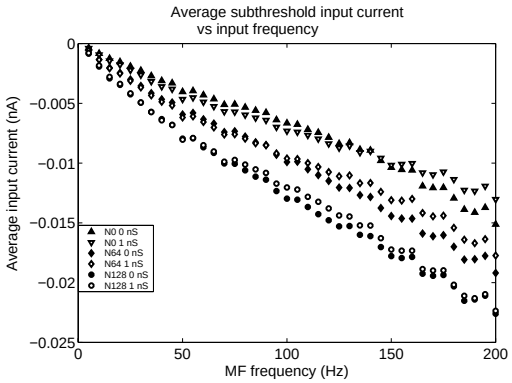

Figure 2

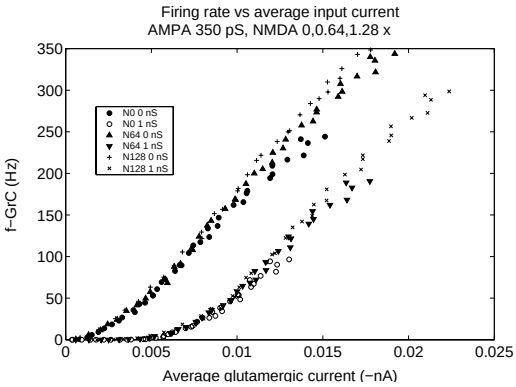

Figure 3

conductances being 64 % (N64) and 128 % (N128) the value of the AMPA peak conductance.

All simulation data points could be well fitted with low order polynomials.Without shunting inhibition the input-output relation was even basically linear when NMDA receptors were present and almost linear when absent. The NMDA receptors had a linearizing effect. All curves in the presence of shunting inhibition are nonlinear. They rise in a concave manner and adopt gradually a more linear character, attaining asymptotically the same slope as that of the non-shunting case. The overall gain was greatly enhanced as a result of the addition of NMDA receptors.

The width of the concave regime determines where divisive gain modulation is possible. Derivatives of the polynomial fits showed that the configuration with a higher percentage of NMDA receptors lost at a higher rate their divisive gain modulation capabilities. For mossy fiber frequencies higher than 100 Hz the difference between the +1 nS slope and the +0 nS slope (with the same output frequency) became less than 25 % in the N64 case, for the N128 case this already occurred at 70 Hz. Without NMDA receptors the slope difference amounted at a mossy fiber frequency of 200 Hz still more than 40 %. Concomitantly, the mossy fiber frequencies needed to produce a non-zero output firing rate (offset) diminish with an increasing amount of NMDA receptors.

Adding NMDA receptors to the system increases the total synaptic input current to the cell and its temporal characteristics. Which of these is mainly responsible for reducing the range of input frequencies where gain modulation is possible?

A comparison of the average subthreshold input currents at different frequencies is shown in figure 2. In the N0 case the average current increased approximately linearly with the input frequency, whereas in the other cases the current increases slightly stronger for the lower input frequencies.

In figure 3 the output frequency of the granule cell is plotted as a function of the average subthreshold input currents in the three different configurations. Although the temporal characteristics were changed in the N64 and N128 cases (the coefficient variation of the input currents was reduced by 20-50% at all frequencies), the output frequency-input current relations were nearly identical. This suggests that the amount of concavity of the +1 nS ff-curves and subsequently the range of input frequencies which allow gain modulation, is largely determined by the input frequency-input current relationship.

4. Discussion

NMDA-receptor mediated currents do not prevent gain modulation by shunting inhibition in granule cells. The range of mossy fiber input frequencies that allow effective gain modulation becomes however more restricted depending upon the amount of NMDA receptors. Extrasynaptic NMDA receptors, which were not modelled in this study, could further limit the bandwidth. Beneficial for gain modulation at low frequencies is that the subtractive gain (offset) is reduced. The different response properties in the presence of NMDA recptors were mainly attributable to the increased amount of subthreshold synaptic current and not to the changed temporal characteristics of the input current.

Acknowledgements

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References

[1] E.D. D'Angelo, G. DeFilippi, P. Rossi, V. Taglietti, Synaptic excitation of individual rat cerebellar granule cells in situ: evidence for the role of NMDA receptors, J. Physiol., 484 (1995) 397-413

[2] L. Cathala, S. Brickley, S. Cull-Candy, M. Farrant, Maturation of EPSCs and intrinsic membrane properties enhances precision at a cerebellar synapse, Journal of Neuroscience, 23 (2003) 6074-6085.

[3] F.S. Chance, L.F. Abbott, Gain modulation from background synaptic input, Neuron, 35 (2002) 773-782.

[4] P.J. Drew, L.F. Abbott, Model of song selectivity and sequence generation in area HVc of the songbird, J. Neurophys., 89 (2003) 2697-2706.

[5] G.R. Holt, C. Koch, Shunting inhibition does not have a divisive effect on firing rates, Neural Computation, 9 (1997) 1001-1013.

[6] P.L. van Kan, A.R. Gibson, J.C. Houck, Movement related inputs to intermediate cerebellum of the monkey, J. Neurophys., 69 (1993)

[7] R. Maex, E. DeSchutter, Synchronization of Golgi and granule cell firing in a detailed network model of the cerebellar granule cell layer, Journal of Neurophys., 80 (1998) 2521-2537.

[8] S. J. Mitchell, R.A. Silver, shunting inhibition modulates neuronal gain during synaptic excitation, Neuron, 38 (2003) 433-445.

[9] C.I.O. Myme, K. Sugino, G.G. Turrigiano, S.B. Nelson, The NMDA-to-AMPA ratio at synapses onto layer 2/3 neurons is conserved across prefrontal and visual cortices, J. Neurophys., 90 (2003) 771-779.

[10] P. Rossi, NMDA receptor 2 (NR2) C-terminal control of NR open probability regulates synaptic transmission and plasticity at a cerebellar synapse, Journal of Neuroscience, 22 (2002) 9687-9697.

[11] E. Salinas, P. Thier, Gain modulation: a major computation principle of the central nervous system, Neuron, 27 (2000) 15-21.

[12] L.Y. Wang, The dynamic range for gain control of NMDA receptor-mediated synaptic transmission at a single synapse, J. Neuroscience, 20 (2000) 115RC.