CNS 2003, Alicante, Spain

TITLE: A computational study of the modulation of the extrasynaptic GABAA conductance in cerebellar granule cells

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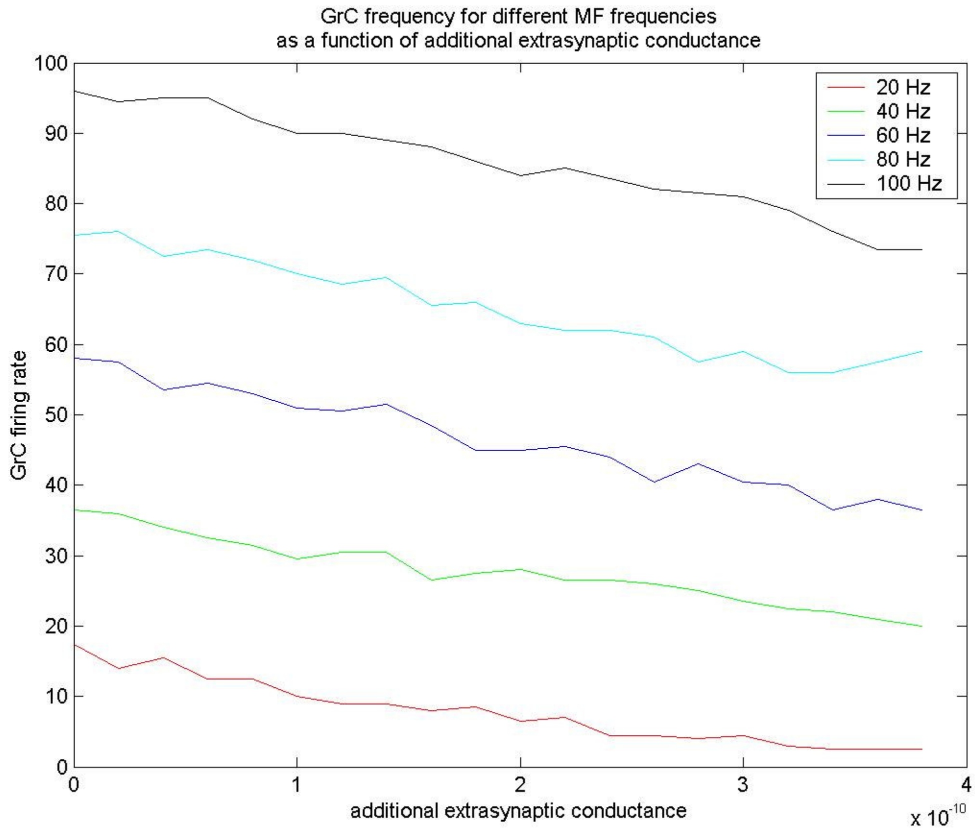
ABSTRACT:
Granule cells in the cerebellum contain extrasynaptic GABAA receptors whose conductance is amenable to modulation. In this study it is shown that increasing this conductance prolongs the period of effective non-excitability of a granule cell, after it has received inhibition from a Golgi cell. On the network level it is seen that modulation of this conductance can reduce the probability of granule cell spiking. However the timing of granule cell spikes, if they occur, is unaffected.

KEYWORDS: glomerulus, granule cell, Golgi cell, GABA

SUMMARY:

In the granular layer of the cerebellar cortex mossy fiber axons make excitatory synapses onto granule cell dendrites within structures called glomeruli. In addition the glomeruli contain inhibitory synapses between Golgi cell axons and granule cell dendrites.
Within a glomerulus the synapses are tightly packed and the whole structure is enveloped by a tight glial sheath. Both of these characteristics increase the likelihood that neurotransmitters which diffuse out of the synaptic cleft cause activation of neighboring receptors.
The inhibition of granule cells by Golgi cells is mediated by GABAA receptors located within the synapse. Furthermore granule cells contain extrasynaptically located GABAA receptors. These receptors mediate the spillover component of the Golgi-cell evoked inhibition of granule cells (1). In addition these receptors are, even in the absence of Golgi spikes, tonically activated, with a conductance of approximately 200 pS (2).
The current transferred by the tonic part of the extrasynaptic conductance is estimated to be about ¾ of the total inhibitory current, measured under the condition of high-frequency spiking of Golgi cells. Of the spike-evoked inhibitory current, 89% is due to the spillover component. Thus, the extrasynaptic conductance is responsible for 97% of the IPSC charge transfer (1).
Therefore it is clear that the extrasynaptic conductance plays an important role and that modulation of its strength could have interesting consequences.
It has been reported that the size of the extrasynaptic conductance can be modulated by up to four times its original value under the influence of acetylcholine (3).
This study investigates what the consequences of this modulation are, first on the level of a single cell, and subsequently on the network level.
A conductance-based model was used to describe the properties of the granule cell (4,5).
First the relationship between the mossy fiber input firing rate (consisting of 4 mossy fibers, firing independently as a Poisson process), and the granule cell firing rate was

studied, as a function of the level of extrasynaptic conductance. Increasing this conductance resulted in a similar decrease of the granule cell frequency for all mossy fiber input frequencies (see figure 1). This is similar to the results obtained in an experimental study (6), where only instead of mossy fiber input a direct current injection was used.



Next the influence of the strength of the extrasynaptic conductance on the average time to the first spike of the granule cell after a Golgi cell firing was investigated as a function of different mossy fiber input frequencies.

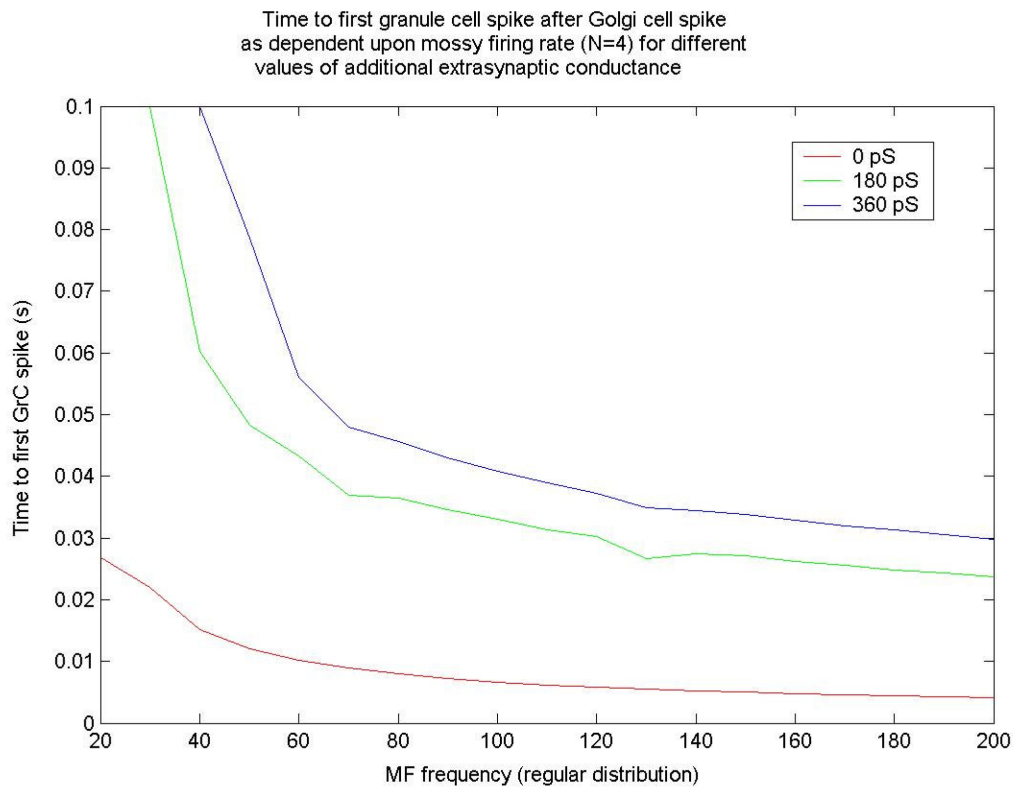


Figure 2 shows that increasing the extrasynaptic conductance results in a longer time to the first granule cell spike, for the whole range of mossy fiber input frequencies. Furthermore it is seen that the time to the first granule spike is much more strongly dependent upon the mossy fiber input frequency for the low frequencies than for the high frequencies. For higher values of the extrasynaptic conductance the range of low frequencies, where this strong dependence exists, is broader.
Might modulation of the extrasynaptic conductance therefore determine the range of input frequencies filtered out? And what will be the effects on the network level?
In order to test this a model of the granular layer was constructed. In the most simple case of the model, the parallel fibers contact all Golgi cells on their route, and in this way close synchrony of Golgi cell firing is achieved. Without modulation of the extrasynaptic conductance, this leads to similar inhibitory input to all granule cells. With modulation one might expect that granule cells with a stronger extrasynaptic conductance fire with a longer delay.
Careful tuning of the granule spike timings by means of modulation of the extrasynaptic conductance could be computationally quite interesting.
However initial simulations don't show an effect on the timing of granule cell spikes. It is seen that spiking of granule cells can be reduced or even completely suppressed, if their extrasynaptic conductance is increased.But when these granule cells with increased conductance spike, it is with the same delay as their unmodulated counterparts. This seems in disagreement with the above-mentioned single cell study. Further work is in progress to explain this discrepancy.

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