ABSTRACT

Inhibitory GABAergic neurons, although forming a minor proportion of the neuronal population in the central nervous system, have been reported to be crucial for different physiological states of the brain. Among the vast diversity of this neuronal subpopulation, the fast spiking interneurons (FSINs) have been studied in great detail owing to their morphological and physiological attributes and functional correlates. Due to their perisomatic targeting and rapid spiking nature, they have been strongly associated with spike time and gain control of their target neurons in neuronal microcircuits across different regions of the brain. Plastic alterations of neuronal synaptic and intrinsic properties have been associated with learning and memory. However, a vast majority of the studies performed so far pertains to excitatory neurons. Although some recent studies have looked into plasticity of inhibition, little is known about plastic changes in the inhibitory neurons. Owing to the morpho-physiological properties of the FSINs and their massive connectivity, plastic alterations in them can cascade to their connected neuronal microcircuit.

The dentate gyrus (DG) forms an important gateway of information for the hippocampus and has been associated with pattern separation. The granule cells which are predominantly known to target interneurons discharge in the gamma frequency range. Hilar interneurons including the FSINs are known to show membrane potential oscillations phase-locked with the extracellularly recorded oscillations. However, the consequent response of a FSIN to repetitive excitatory gamma synaptic bursts presented either in isolation or in association with membrane potential

modulations has not received attention. We show that the FSINs of the DG sub field express a robust long lasting decrease in intrinsic excitability after experiencing bursts of synaptic stimulation of the mossy fiber pathway at gamma frequency (30 Hz), repeated at delta (2 Hz) or theta frequency (4 Hz). Interestingly, the GCs did not express any plasticity of intrinsic excitability upon experiencing similar gamma bursts repeated at delta frequency. The change in intrinsic excitability in the FSINs was observed to be strongly dependent on the somatic current supplement that altered the membrane potential in phase with the synaptic gamma bursts. The plasticity was found to be dependent on the post synaptic calcium flux through the calcium-permeable AMPA receptors (CP-AMPARs) and also on post synaptic HCN channel conductance. Further, decreased excitability in the FSINs exhibited decreased inhibition in the post-synaptic putative granule cells. Additionally, we have used network simulations to predict that the spiking rate of an excitatory neuron is strongly dependent on the intrinsic excitability of a perisomatic targeting interneuron; both integrated in a feedback microcircuit.

Given the importance of FSINs in network synchronization, understanding how intrinsic excitability and its plasticity in the FSINs can affect the network attributes is of seminal interest in the field of neuronal circuit dynamics and plasticity. We used computational simulation of physiologically scaled down neuronal networks consisting of experimentally constrained models of neurons to address this question. Intrinsic excitability in FSINs has been experimentally observed to be altered due to changes in their input resistance and changes in their action potential threshold. To alter the input resistance of the FSINs, we changed the specific membrane resistance (R_m), while to change the action potential threshold we altered the peak delayed potassium conductance (g_{KD}bar) In Wang-Buzsaki type FSIN-FSIN interconnected network

models (II network) we observed an increase in the network frequency with increase in FSIN R_m while the network coherence did not change due to the altered FSIN R_m. However, in the same network there was a drastic decrease in both network coherence and network frequency with increase in g_{KD}bar. Next, we built an EI network using 250 model excitatory neurons (ENs) and 50 model FSINs. The ENs were reciprocally connected to the FSINs. Moreover, the FSINs were also interconnected among themselves while the ENs were not. In these EI networks we observed that decreased FSIN R_m, which decreased their excitability, caused a monotonic increase in the excitatory network coherence. However, increased FSIN g_{KD}bar which also decreased their excitability caused a decrease in the excitatory network coherence. The excitatory network frequency was decreased with decreased FSIN R_m or with increased FSIN g_{KD}bar. However, EI networks having decreased FSIN input resistance (~ 50 MΩ) could partially rescue the excitatory network coherence from the desynchronizing effect of increased FSIN g_{KD}bar. In EI networks having higher FSIN input resistance (~ 110 MΩ); even a small increase in FSIN g_{KD}bar caused a drastic decrease in the excitatory network coherence. The phenomenon of altered EI network activity due to altered FSIN R_m or FSIN g_{KD}bar was observed to be significantly independent of the proportion of the FSIN population undergoing the alterations. The observation that even a small proportion of the entire FSIN population (10% and 40%; for FSIN R_m dependence and FSIN g_{KD}bar dependence respectively) can cause a massive shift in the EI network activity indicated the strong influence of FSIN intrinsic excitability on network dynamics. We also observed that the dependence of FSIN R_m on EI network activity was quite robust in the physiological range of the network synaptic parameters.

Overall from these studies we observed that DG FSINs express activity dependent plasticity of intrinsic excitability after experiencing near physiological synaptic excitation. Further, altered intrinsic excitability of FSINs can cause robust changes in the connected network. The study suggests possible intrinsic strategies in FSINs which might be functional in neuronal microcircuits during different physiological and pathological conditions.