Abstract

GABA is the major inhibitory neurotransmitter in the central nervous system. It binds to two types of receptors – ionotropic $GABA_A$ and metabotropic $GABA_B$. The $GABA_A$ receptor directly gates a Cl^- ionophore that causes hyperpolarization in mature excitatory neurons while $GABA_B$ receptor mediates a slower hyperpolarizing response *via* G- protein coupled receptor (GPCR) activated potassium channels. This signaling mechanism gets further complicated by the heterogeneous GABA receptor subunit composition that influences the response kinetics in the postsynaptic membrane. In this thesis, the focus has been to decipher the role of $GABA_A$ receptors in relation to cellular excitability in the subiculum under physiological and pathophysiological conditions.

The subiculum, considered as the output structure of hippocampus, modulates information flow from hippocampus to various cortical and sub-cortical areas and has been implicated in learning and memory, rhythm generation and various neurological disorders. It gates hippocampal activity with its well orchestrated and fine tuned intrinsic and local network properties. Over the years many studies have shown the involvement of subiculum in temporal lobe epilepsy where it forms the focal point of epileptiform activities with altered cellular and network properties. The subiculum is characterized by the presence of a significant population of burst firing neurons that lead local epileptiform activity. By virtue of its bursting nature and recurrent connections, it is a potential site for seizure generation and maintenance. Epileptiform activities are dynamic in nature and change temporally and spatially according to the alterations in electrophysiological properties of neurons. Transitions to different electrical activities in neurons following a prolonged challenge with epileptogenic stimulus have been shown in other brain structures, but not in the subiculum. Considering the importance of the subicular burst firing neurons in the propagation of epileptiform activity to the entorhinal cortex, we have explored the phenomenon of electrophysiological phase transitions in the burst firing neurons of the subiculum in an *in vitro* brain slice model of epileptogenesis.

Whole-cell patch clamp and extracellular field recordings revealed a distinct phenomenon in the subiculum wherein an early hyperexcitable phase was followed by a late suppressed phase upon continuous perfusion with epileptogenic 4-amino pyridine and magnesium-free medium. The late suppressed phase was characterized by inhibitory post-synaptic potentials (IPSPs) in pyramidal excitatory neurons and bursting activity in local fast spiking interneurons at a frequency of 0.1- 0.8 Hz. The IPSPs were mediated by $GABA_A$ receptors that coincided with excitatory synaptic inputs to attenuate action potential discharge. These IPSPs ceased following a cut between the CA1 and subiculum. Our results suggest the importance of feedforward inhibition in the suppression of epileptiform activity in subiculum to mediate a homeostatic response towards the induced hyper-excitability.

GABA release from presynaptic nerve endings activates postsynaptic $GABA_A$ receptors, which evoke faster phasic inhibitory postsynaptic currents (IPSCs) and non-inactivating inhibitory tonic current, mediated through extrasynaptic $GABA_A$ receptors. These receptors are heteropentameric GABA-gated channels assembled from 19 possible subunits (α1-6, β1-3, γ1-3, δ, π, ρ1-3, θ, and ε). The 2 major subunits involved in tonic $GABA_A$ currents in the hippocampus are α5 and δ subunits. Tonic $GABA_A$ receptor mediated inhibitory current plays an important role in neuronal physiology as well as pathophysiology such as mood disorders, insomnia, epilepsy, autism spectrum disorders and schizophrenia. While the alterations of various electrical properties due to tonic inhibition have been studied in neurons from different regions, its influence on intrinsic subthreshold resonance in pyramidal excitatory neurons having hyperpolarization-activated cyclic nucleotide-gated (*HCN*) channels is not known. In the present study, we show the involvement of α5βγ $GABA_A$ receptors in mediating picrotoxin sensitive tonic current in subicular pyramidal neurons using known pharmacological agents that target specific $GABA_A$ receptor subunits. We further investigated the contribution of tonic conductance in regulating subthreshold electrophysiological properties using current clamp and dynamic clamp experiments. Our experiments suggest that tonic GABAergic inhibition can actively modulate subthreshold properties of subicular pyramidal neurons including resonance due to *HCN* channels that may potentially alter the response dynamics in an oscillating neuronal network.