ON HOW EXCITABILITY AND INHIBITION IN THE CORTICAL NETWORK MODULATE SPONTANEOUS SLOW RHYTHMS

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Ferret cortical slices *in vitro* generate a slow oscillatory rhythm when bathed in an ACSF that mimicks ionic concentrations *in vivo* (Sanchez-Vives and McCormick, 2000). This rhythm consists in the alternation between active and silent episodes (up and down states) and is almost identical to a slow (< 1 Hz) cortical oscillation that occurs during slow wave sleep (Steriade et al., 1993). Previous investigations (Sanchez-Vives and McCormick, 2000) have shown that these periods of activity travel along the slice and are sustained by recurrent synaptic input. It was also observed that the blockade of inhibition results in epileptiform activity that propagates an order of magnitude faster than the slow oscillation. However, the precise network mechanisms by which the slice sustains and regulates this activity are largely unknown. A computational network model has been proposed that reproduces remarkably well the electrophysiological observations (Compte et al., 2003) and allows a systematic testing of experimental hypothesis regarding the cortical mechanisms at play in this phenomenon. This model consists of 1024 excitatory cells and 256 inhibitory cells modeled with detailed Hodgkin-Huxley-type channels and interconnected through realistic synaptic dynamics. Critical for the model behavior are strong recurrent excitation and inhibition, and Ca^{2+}- and Na^{+}-dependent potassium channels in pyramidal cells, which are responsible for the transitions between up and down states. Motivated by some results from model simulations, we have studied how the intrinsic excitability of neurons and the strength of recurrent inhibition in the network contribute in determining the duration of the up states, the frequency of the oscillation and the propagation speed across the slice. For that purpose, we combined dual extracellular *in vitro* cortical recordings with computational simulations in the cortical network model of Compte et al. (2003). We modulated the intrinsic excitability of the neurons experimentally by means of changes in potassium concentration (2.5 - 5.5 mM). Extracellular solutions with higher potassium concentrations induced significant reductions in both the duration of the up states and the interval between oscillations, more markedly in the latter than in the former. This result confirmed a prediction of the model, based on its assumption that the slow oscillation is reflecting the build-up and recovery of spike frequency adaptation intrinsic currents in a network that is recurrently connected with strong enough positive feedback so as to sustain spiking reverberation. Extracellular potassium modifications do not only modify the resting potential of the neurons, but also the influence of voltage-dependent potassium channels and spike frequency adaptation currents. Also, potassium might differentially affect distinct neuronal populations in the cortical network. We used the artificial network to assess how these factors (changes in the membrane leak properties, changes in voltage- or activity dependent potassium currents, and increased excitability of the excitatory, the inhibitory or the neuronal population as a whole) mediate the changes in the slow oscillation dynamics observed under increases in excitability. To test the role of inhibition in the determination of the time course and speed of the slow rhythm propagation, increasing concentrations of $GABA_A$ blockers (bicuculline or SR95531, 25 nM - 50 µM) were bath applied. Unexpectedly, decreasing inhibition shortened the duration of the up states. This same result was obtained when reducing inhibition in the artificial network, and is explained by the fact that weaker inhibition results in higher firing rates in pyramidal neurons during

the up state, so that activity dependent potassium currents accumulate faster and force an early termination of the up state. On the other hand, a progressive blockade of inhibition gradually increased the speed of propagation to the typical velocity of epileptiform discharges. A continuous analysis of the extracellular recordings with a sliding window cross-correlogram (50 s) showed a detailed time course of the velocity of activity propagation with the changes in inhibition strength. Every increase in inhibition blockade was followed by an overshoot in propagation speed that in a few minutes decreased to a lower steady level, suggesting that a sudden decrease in inhibition brings the network to a non-stationary level until the excitatory / inhibitory balance is readjusted and the speed is decreased to a steady state for that level of inhibition. When a critical blockade of inhibition is reached the oscillations become an epileptic discharge and a stable speed (average 100 m/s) is reached, that will not increase with further increases in the blockade. This modulation of the propagation speed under partial inhibition blockade was also investigated in the framework of the computational network model.

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