CURRENT LITERATURE

THALAMOCORTICAL CIRCUITS AND EXCITABILITY

Corticothalamic Inputs Control the Pattern of Activity Generated in Thalamocortical Networks

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Absence seizures (3–4 Hz) and sleep spindles (6–14 Hz) occur mostly during slow-wave sleep and have been hypothesized to involve the same corticothalamic network. However, the mechanism by which this network transforms from one form of activity to the other is not well understood. Here we examine this question using ferret lateral geniculate nucleus slices and stimulation of the corticothalamic tract. A feedback circuit, meant to mimic the cortical influence in vivo, was arranged such that thalamic burst firing resulted in stimulation of the corticothalamic tract. Stimuli were either single shocks to mimic normal action potential firing by cortical neurons or high-frequency bursts (six shocks at 200 Hz) to simulate increased cortical firing, such as during seizures. With one corticothalamic stimulus per thalamic burst, 6–10 Hz oscillations resembling spindle waves were generated. However, if the stimulation was a burst, the network immediately transformed into a 3–4 Hz paroxysmal oscillation. This transition was associated with a strong increase in the burst firing of GABAergic perigeniculate neurons. In addition, thalamocortical neurons showed a transition from fast (100–150 msec) IPSPs to slow (approximately 300 msec) IPSPs. The $GABA_B$ receptor antagonist CGP 35348 blocked the slow IPSPs and converted the 3–4 Hz paroxysmal oscillations back to 6–10 Hz spindle waves. Conversely, the $GABA_A$ receptor antagonist picrotoxin blocked spindle frequency oscillations resulting in 3–4 Hz oscillations with either single or burst stimuli. We suggest that differential activation of thalamic $GABA_A$ and $GABA_B$ receptors in response to varying corticothalamic input patterns may be critical in setting the oscillation frequency of thalamocortical network interactions.

Cortical Feedback Controls the Frequency and Synchrony of Oscillations in the Visual Thalamus

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Thalamic circuits have an intrinsic capacity to generate state-dependent oscillations of different frequency and degrees of synchrony, but little is known of how synchronized oscillation is controlled in the intact brain or what function it may serve. The influence of cortical feedback was examined using slice preparations of the visual thalamus and computational models. Cortical feedback was mimicked by stimulating corticothalamic axons, triggered by the activity of relay neurons. This artificially coupled network had the capacity to self-organize and to generate qualitatively different rhythmical activities according to the strength of corticothalamic feedback stimuli. Weak feedback (one to three shocks at 100–150 Hz) phase-locked the spontaneous spindle oscillations (6–10 Hz) in geniculate and perigeniculate nuclei. However, strong feedback (four to eight shocks at 100–150 Hz) led to a more synchronized oscillation, slower in frequency (2–4 Hz) and dependent on $GABA_B$ receptors. This increase in synchrony was essentially attributable to a redistribution of the timing of action potential generation in lateral geniculate nucleus cells, resulting in an increased output of relay cells toward the cortex. Corticothalamic feedback is thus capable of inducing highly synchronous slow oscillations in physiologically intact thalamic circuits. This modulation may have implications for a better understanding of the descending control of thalamic nuclei by the cortex, and the genesis of pathological rhythmical activity, such as absence seizures.

COMMENTARY

These studies evaluated whether cortical output can promote synchrony in the thalamic circuit, as had been predicted from theoretical models. At issue are the mechanisms

through which seizures develop in generalized absence epilepsy.

Both groups used an innovative approach to evaluate how cortical circuits might modify oscillatory activity in isolated slices of ferret thalamus. Because it is impractical to maintain robust synaptic connectivity between cortical and thalamic structures in vitro, special electronic circuitry was constructed to produce an artificial cortex that would respond to thalamic electrical activity with appropriately timed "cortical" responses. These, in turn, were reflected back to the thalamic circuit through extracellular stimulation of corticothalamic fiber tracts. Experiments tested whether increases in cortical excitability, for example, an increased number of cortical neuronal action potentials triggered by each thalamic volley, would influence the degree of synchrony in thalamus.

Cortical feedback in the form of a single-action potential response to each thalamic volley resulted in a slight enhancement of the control (cortex-disconnected) 6–10 Hz spindle-like oscillation in the thalamic network. In contrast, a larger number of cortical responses, for example, six spikes per thalamic volley, resulted in a transformation of the thalamic network into a slower (3 Hz), more synchronous activity that resembles that observed in absence seizures. This seizure-like response was associated with a large increase in synaptic activation of perigeniculate neurons, which are the functional equivalent to thalamic reticular neurons. The hypersynchronous thalamic discharges were sensitive to the $GABA_B$ antagonist CGB35348.

Enhanced cortical output, as might occur for example during cortical disinhibition, appears to be able to transform normal thalamic rhythmic activity into pathophysiologcial hypersynchronous discharge. This suggests that either cortical or thalamic mechanisms can lead to degeneration of an absence discharge.

Previous in vitro studies by these researchers have shown that $GABA_A$ receptor disinhibition within thalamic circuits can transform spontaneous spindle-like activity related to sleep into a slower 3–4 Hz network activity that resembles the activity of absence epilepsy. These effects appear to be mediated at least in part through a loss of recurrent inhibitory responses between perigeniculate neurons. $GABA_A$ disinhibition is unlikely to explain completely the generation of absence seizures in humans. Therefore, these results are important because they show additional mechanisms in which the thalamic portion of the circuit can be recruited to produce a generalized seizure. Both of these studies show that enhanced "cortical output" was able to entrain the neurons in the perigeniculate nucleus and cause them to fire very prolonged bursts of action potentials. These, in turn, lead to a strong activation of $GABA_B$ receptors in thalamic relay cells and therefore powerful rebound bursts that recurrently drive the intrathalamic circuit. These data suggest that cortical input has the capability of overpowering the normal recurrent inhibitory connections between perigeniculate cells and suggest an additional mechanism for development of absence seizures. Furthermore, they suggest that the corticothalamic excitatory connections into the inhibitory projection neurons of the thalamus, those in the reticular thalamic nucleus, or the equivalent perigeniculate nucleus, are a potential site at which pharmacological treatment of absence epilepsy might be targeted. For example, glutamatergic antagonists that would reduce corticothalamic input into perigeniculate neurons might decrease the ability of the thalamic circuit to generate the hypersynchronous discharge of an absence seizure.

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