Presentation Abstract

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Presentation Title: Role of 5HT2 and 5HT3 receptors in the generation of epileptiform activity: In vitro, in silico and In vivo studies

Location: Halls B-H

Presentation time: Sunday, Nov 10, 2013, 4:00 PM - 5:00 PM

Topic: ++B.09.d. Oscillations and synchrony: Other

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Abstract: The broad expression of serotonin (5-HT) receptors in the neocortex is juxtaposed with dense innervation by serotonergic afferents, underscoring the influence of 5-HT on cortical activity. While the effects of 5-HT are well understood at the level of the neuron, its role in network activity remains unclear. We have shown that elevating 5-HT in disinhibited cortical slices with the selective serotonin reuptake inhibitor, fluoxetine (FLX), transforms cortical network dynamics from single bursts, known as paroxysmal depolarizing shifts (PDS), to periodic (15 Hz) burst clusters known as paroxysmal fast runs (PFRs), a form of activity often seen in animal and human epileptic seizures. The emergence of PFRs depends on 5-HT2 receptors (5-HT2Rs) as they are blocked by ketanserin (KSN). We set out to investigate the mechanistic underpinnings of the 5HT2R-dependent switch from temporally random and sparse to periodic and clustered network bursts. To this end, we measured postsynaptic currents during network events in control and FLX-treated cortical slices and observed an increase in excitatory and a decrease in the inhibitory postsynaptic currents (EPSCs & IPSCs). KSN reduced the enhanced EPSCs to control levels, while further decreasing IPSCs. We confirmed the sufficiency of these changes to the emergence of PFRs using a computer simulation of a model cortical network. Furthermore, since the emergence of PFRs depends on 5-HT2Rs, we tested in vivo whether 5-HT2Rs modulate epileptic seizures, the behavioral correlate of the PFRs observed in vitro. Indeed, injection of KSN before seizure induction with
pentylenetetrazole (PTZ) significantly delayed the onset of epileptic seizures. In parallel with 5-HT2R-dependent modulation of network activity, we also explored the role of 5-HT3 receptors (5-HT3R) in cortical dynamics. We previously showed that FLX enhances spontaneous synaptic activity through 5-HT3Rs in cortical neurons. Blocking 5-HT3Rs with granisetron in FLX-treated disinhibited slices results in a significant reduction of network bursts, though the emergence of PFRs remains unaffected. Combined, our results present a mechanism by which augmented 5-HT signaling in the cortex alters cortical dynamics: 5-HT2Rs act in concert with 5-HT3Rs on cortical neurons to elevate global levels of excitation, while 5-HT2R activity transforms cortical activity patterns from random bursts to highly periodic fast runs of paroxysmal discharges. These findings emphasize the importance of neuromodulatory control in shaping cortical dynamics and provide a potential therapeutic avenue for treating epileptic seizures that are resistant to typical antiepileptic drugs.

**Disclosures:**  
**P.A. Puzerey:** None. **R. Fernández Galán:** None.

**Keyword(s):**  
SEROTONIN  
EPILEPSY  
NEOCORTEX