Presentation Abstract

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Presentation Title: Serotonergic synaptic transmission modulates network dynamics in the mouse neocortex: Implications for epilepsy

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Abstract: The dense innervation of the neocortical sheath by ascending brainstem projections provides neuromodulatory inputs that influence cortical activity. In particular, the monoamine serotonin (5-HT) exerts an array of excitatory and inhibitory effects on cortical pyramidal cells (PCs). Here, we explore the role of the 5-HT system in modulating synaptic transmission and network dynamics by performing whole-cell patch clamp recordings from cortical layer 2/3 PCs in thalamocortical brain slices from C57BL/6 wild-type (WT) and Pet-1 knockout mice (KO). 5-HT levels are severely reduced in the brain of KO mice, as is the expression of the 5-HT reuptake transporter, SERT. Thus, 5-HT signaling could be diminished or augmented in these mice, depending on whether the deficit in 5-HT synthesis outcompetes the deficit in 5-HT reuptake. To test this, we measured spontaneous excitatory postsynaptic currents (sEPSCs) and observed a significant increase in both amplitude and frequency in KO slices, which was dramatically reduced after adding the 5-HT3 receptor (5-HT3R) antagonist, granisetron, suggesting an increase in synaptic excitatory transmission mediated by 5-HT. Additionally, treatment of WT slices with the selective serotonin reuptake inhibitor (SSRI), fluoxetine (FLX; 3 µM), resulted in a significant increase of sEPSC amplitude and frequency comparable to KO levels. To address whether the observed increase in synaptic activity would correspond to a change in network dynamics, we induced network activity in the form of paroxysmal depolarizing shifts (PDS) by partially blocking GABA(A) receptor-mediated inhibition with bath-applied gabazine (5 µM). WT slices preferably exhibited network activity
in the form of individual PDS, whereas in the KO slices the PDS are grouped into periodic (10-15 Hz) fast runs of network activity. When treated with FLX, WT slices display the same dynamics as the KOs. Remarkably, the occurrence of fast runs is reduced by the 5-HT2 receptor (5-HT2R) antagonist, ketanserin, in KO and FLX-treated WT mice. These findings suggest that 1.) increased excitatory synaptic transmission in KO mice results from increased serotonergic signaling through 5-HT3Rs, and 2.) altered network dynamics in KO and FLX-treated mice are attributable to increased signaling through 5-HT2Rs. Our results demonstrate that synaptic 5-HT signaling in Pet-1 KO mouse is increased, suggesting that the reuptake deficit outcompetes the decreased synthesis and release of 5HT. Furthermore, the increased network excitability due to serotonin reuptake inhibition in WT provides a mechanistic link to the emergence of epileptic episodes in patients medicated with SSRIs.

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

Keyword(s):  
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NETWORK


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