Inhibition Sculpts Neuronal Structure and Function During Adolescence: Implications for Mood and Learning

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Adolescence is a critical period when learning potential changes and certain mental disorders, such as anxiety, emerge. One potential reason for these changes is the α4βδ $GABA_A$ receptor (GABAR) which increases expression in CA1 hippocampus and prefrontal cortex at the onset of puberty for 10 days. This receptor is localized to the soma as well as the dendritic shaft and spine where it impairs activation of NMDA receptors, which are essential for learning and spine maintenance. As a result, induction of hippocampal long term potentiation using theta burst stimulation, an in vitro model of learning, is nearly prevented and spatial learning is impaired. In contrast, LTP and spatial learning are robust in the δ knock-out mouse, implicating α4βδ GABARs in reducing learning potential at puberty. The prelimbic region of the prefrontal cortex increases anxiety. We have shown that synaptic pruning of this region is due to the increased expression of α4βδ GABARs. Local α4 knock-down in the prelimbic, accomplished using the Cre-LoxP system, increased excitatory synapses leading to anxiety behavior, as evidenced by reduced open arm time on the elevated plus maze in adulthood, suggesting that prelimbic pruning is necessary to limit anxiety. Stress may act to dysregulate this system as our recent findings suggest: Unpredictable stress in adolescence increases anxiety in female mice. However, chronic predictable stress improves resilience by decreasing immobility in the forced swim test, an effect dependent upon α4βδ GABARs. These findings suggest that pubertal α4βδ GABARs play a role in altering learning, anxiety and resilience.