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Forced physical training causes increased neuronal survival and maturation with their integration into normal circuits in pilocarpine induced status epilepticus mice

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Statement of the Problem: Increased neurogenesis acutely after Status Epilepticus (SE) is a well-known fact. These increased newly born neurons contribute to the aberrant rewiring of the hippocampus and are hypothesized to promote epileptogenesis. Physical Training (PT), which has been recognized as an effective complementary therapy to treat epilepsy, was also reported to cause more increase in neurogenesis acutely after SE by various studies. Fate and role of these extra newly-born neurons due to PT has remained elusive, whether they integrate in normal circuits or increase aberrant integrations is yet to be determined. Answer to this question will reveal the basic mechanisms by which PT effect epilepsy.

Methodology: We evaluated the effect of four weeks moderate intensity treadmill running PT on adult male Kunming Mice after pilocarpine induced SE. Dividing progenitors were labelled by BrdU at acute stage (1-week after SE) and histological examinations of hippocampal sections were performed for aberrant hippocampal neurogenesis after spontaneous recurrent seizures' monitoring. Changes in genetic methylation of BDNF gene and its level in hippocampus through Western blot analysis were measured at acute stage (2-weeks) after SE to explore underlying pathways which cause increased neurogenesis.

Findings: Although PT increased proliferation in sub-granular zone of dentate gyrus of hippocampus at acute stage after SE but these newly born neurons not only shown more survival (surviving Brdu+ cells) and maturation (BrdU+NeuN stained cells) but they also integrated into normal circuits and shown reduced aberrant hippocampal neurogenesis assessed through decrease in number of ectopic granular cells, hilar basal dendrites and mossy fiber sprouting as compared to non-exercised SE group. Although SE decreased the %age methylation of CpGs of BDNF gene' promoters, PT increased BDNF level through some pathways other than de-methylating BDNF CpGs. Normalized integrations of newly born neurons might resulted in decreased spontaneous recurrent seizures and increased spatial memory assessed through Morris water maze test.

Conclusion & Significance: PT increases hippocampal neurogenesis through increasing BDNF levels by some pathways other than de-methylating BDNF CpGs and causes post SE newly born neurons to integrate into normal circuits thus resulting in decreased spontaneous recurrent seizures and enhanced spatial memory.

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