mTOR signaling pathway and cell proliferation are altered during the development of absence epilepsy in a genetic animal model

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Several studies have demonstrated the involvement of the mammalian target of rapamycin (mTOR) signaling pathway in epilepsy and the process of epileptogenesis[1;2]. The hyperactivation of this pathway in the brain is observable in the initial phase after an epileptogenic insult and, its specific inhibition by rapamycin prevents the development of spontaneous seizures[2;3]. We have recently demonstrated that inhibition of mTOR by rapamycin following an early long-term treatment (started before seizure onset), permanently reduces the number and duration of spontaneous absence seizures in adult WAG/Rij rats, an established genetic animal model of absence epilepsy; furthermore, it was observed that mTOR phosphorylation (a measure of mTOR pathway activation) was significantly increased in the cortex of 6 month-old WAG/Rij rats but not other brain areas (i.e. hippocampus and thalamus)[4]. However, it was not clear whether this hyper-phosphorylation was a cause or a consequence of the absence seizure development in these animals.
Based on this background, we wished to clarify the role of mTOR in epileptogenesis in WAG/Rij rats by analyzing immunohistochemically and therefore we studied: 1) the brain expression levels of total mTOR and its phosphorylated form in young (before seizures) and adult WAG/Rij rats (with absence seizures), compared with age-matched Wistar (seizure-free) rats; 2) the proliferation of hippocampal neuronal stem/progenitor cells assessed by BrdU analysis at different ages in both strains. We found that WAG/Rij rats have higher levels of total mTOR expression in several brain areas than control Wistar rats; furthermore, phospho-mTOR (activated pathway) staining is higher in young WAG/Rij rats in comparison to control and adult WAG/Rij rats. Finally, the age-related decline in hippocampal neural progenitor cell proliferation rate was significantly slower in WAG/Rij rats compared to Wistar rats, indicating a change (possibly protective) in proliferation characteristics. Our results support a role for persistent mTOR activation and consequent change in hippocampal progenitor cell proliferation during the epileptogenic process leading to the development of absence seizures in WAG/Rij rats.
References

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