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Investigating the Cardiovascular Changes in Rat Model of Lithium-Pilocarpine Induced Spontaneous Recurrent Seizures

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Abstract

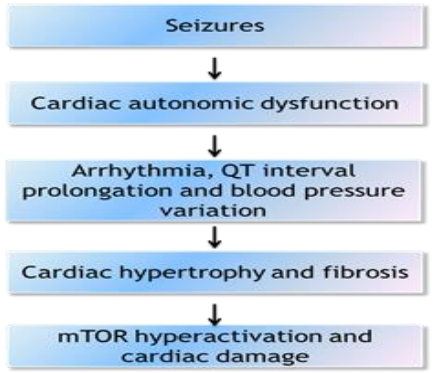
Background: Epilepsy is a chronic neurological condition that is mainly characterized by occurrence of spontaneous recurrent seizures. Study has also shown that temporal lobe seizure lead to development of ventricular fibrillation, shortening or prolongation of QT intervals, producing prolongation in the action potential, propensity to malignant tachyarrhythmia's thus risking cardiac damage. These cardiac repercussions often lead to life-threatening condition known as "Sudden Death in Epilepsy or SUDEP".

Methods: The present study was envisaged to understand the cardiac changes during different phases of epileptogenesis and molecular changes in rat lithium-pilocarpine (Li-pilo) model of epilepsy. The animals were exposed to Li-pilo for induction of spontaneous recurrent seizures (SRS). Non-invasive blood pressure and electrocardiography was recorded at 7th, 28th and 75th day after pilocarpine administration, considered as latent, initial SRS and late SRS phases, respectively. Following electrocardiography on the day 75, blood was collected for serum biochemistry and animals were sacrificed for cardiac histopathology, specific protein levels and gene expression.

Findings: Latent mean arterial pressure decreased as compared to the basal, whereas it was increased during initial and late SRS phases. Prolonged QTc interval was observed during late SRS as that of basal and latent phase. A significant increase in the serum level of lactate dehydrogenase and creatine kinase was observed in epileptic animals, along with hypertrophy, degenerative changes and fibrosis in heart sections. Increase in the expression of TGF-β, S6 ribosomal, phospho-S6 ribosomal, HIF-1α, Na+/K+-ATPase α1, collagen I, mTOR and phospho-mTOR proteins was observed in the cardiac tissue. The cardiac mRNA level of HIF-1α, mTOR, Rps6, Scn1b, Scn3b, Nav1.5 and TGF-β was also increased as compared to control.

Conclusion: The results concluded that Li-pilo-induced SRS leads to cardiac dysfunction via mTOR pathway upregulation, thus suggested the regulatory control of mTOR pathway as a potential target for SUDEP management.

Graphical abstract:



Biography:

Supriya Sharma is a senior Ph.D. scholar, working in the area of pharmacology, specifically in epilepsy and associated cardiac damage. She has expertise in molecular biology and has established a chronic epilepsy associated cardiac damage model in the lab. Through this study she is trying to decipher the associated molecular mechanisms of sudden death in epilepsy (SUDEP). She has five years of experience in this field and seven years of research exposure. In addition, she has also established the zebrafish model for the same condition for further understanding the SUDEP pathophysiology.

Speaker Publications:

1. Scorza FA, Arida RM, Cysneiros RM, et al. The brain-heart connection: implications for understanding sudden unexpected death in epilepsy/Cardiol J 2009/16(5): 394-9.

2. Hernández G, Lal H, Fidalgo M, et al. A novel cardioprotective p38-MAPK/mTOR pathway. Exp Cell Res 2011/ 317(20): 2938-49.
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4. Ravindran K, Powell KL, Todaro M, O'Brien TJ. The pathophysiology of cardiac dysfunction in epilepsy. Epilepsy Res 2016/127:19-29.
5. Mazumder AG, Sharma P, Patial V, Singh D. Ginkgo biloba L. attenuates spontaneous recurrent seizures and associated neurological conditions in lithium-pilocarpine rat model of temporal lobe epilepsy through inhibition of mammalian target of rapamycin pathway hyperactivation. J Ethnopharmacol 2017/204: 8-17.

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