METABOLIC ALTERATIONS PREDISPOSE TO EPILEPSY IN HIGH FAT DIET TREATED MICE

Valentina Nesci[1], Biagio Arcidiacono[1], Rita Citraro[1], Antonio Leo[1], Emilio Russo[1], Antonio Brunetti[1], Giovambattista De Sarro[1]

[1]Department of Health Science, School of Medicine, University Magna Graecia of Catanzaro, Catanzaro - Italy

Introduction: Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures often associated with neuropsychiatric comorbidities. Metabolic disorders seem also to be related with epilepsy, but the mechanism underlying this relationship remains still unclear. Aim of this study was focused on the evaluation of seizure susceptibility in an experimental model of type 2diabetes mellitus (T2DM) and to study the comorbidities and the molecular mechanisms involved.

Materials and methods: Four-week-old male CD1mice were fed with standard laboratory chow (NCD) or High Fat Diet (HFD) containing 59% kcal fat, 15% kcal protein and 25% kcal carbohydrate up to the development of metabolic syndrome, which was also evaluated by intraperitoneal glucose tolerance test (IPGTT) and insulin tolerance test (ITT) in both HFD and NCD groups. After this period, a sub-convulsive dose of PTZ (30mg/kg/i.p.) was injected, every other day, to induce kindling in HFD and NCD mice. Furthermore, a group of HFD and NCD mice, were also treated with metformin (300 mg/kg), in order to evaluate its impact on PTZ-kindling progression. Mice were considered fully kindled when exhibiting 3consecutive stage 5seizures. Likewise, in the same experimental groups several behavioral tests such as, open field test (OFT), forced swimming test (FST), passive avoidance (PA) and Morris water maze (MWM) were respectively performed to study anxiety- and depressive-like behavior as well as learning and memory. Western Blot analysis was also carried out to study GLUT-1and GLUT-3carriers in the brain.

Results: HFD mice groups (HFD and HFD-kindled) showed a significant ($p < 0.01$) weight gain in comparison to their respective controls. Metformin treatment, in HFD mice groups, was able to significantly ($p < 0.01$) prevented body weight gain. HFD mice develop stage 5seizures in the PTZ kindling model faster than age matched NCD control mice. Metformin treatment significantly ($p < 0.01$) delayed kindling development in NCD and HFD mice groups. Moreover, HFD mice groups showed an anxiety-like behavior as well as cognitive impairment in comparison both to NCD mice and metformin HFD mice groups. Our molecular analysis evidenced that HFD reduce GLUT-1expression. PTZ-kindling reduced GLUT-1levels in NCD mice while increasing its expression in HFD mice. GLUT-3was increased by both HFD and PTZ-kindling. Finally, metformin normalized GLUT-1and GLUT-3expression in all groups.

Discussion and conclusions: Our results demonstrate that metabolic syndrome increased seizure susceptibility and their related neuropsychiatric comorbidities. Further studies are needed to clarify the exact mechanism(s) by which metabolic syndrome is linked to epilepsy and how metformin exerts these beneficial effects.