

Neuroprotective Effects of ROCK Inhibition on Hippocampal Energy Metabolism in a Rat Model of Metabolic Syndrome

Otari bibilashvili

e-mail: otar.bibilashvili@tsu.ge

Department of Biology, Iv. Javakhishvili Tbilisi State University, Tbilisi, Georgia

Metabolic syndrome (MS) is characterized by insulin resistance, hyperglycemia, and dyslipidemia, which collectively disrupt neuronal energy metabolism and impair hippocampal function. Rho-associated kinase (ROCK) has been implicated in neuroinflammatory and metabolic dysregulation, but its role in MS-induced hippocampal dysfunction remains incompletely understood. This study investigated whether ROCK inhibition by fasudil restores hippocampal energy metabolism in a rat model of fructose-induced metabolic syndrome.

Male Lewis rats were divided into control, MS, and MS+fasudil groups. Histological and biochemical analyses revealed that MS disrupted glucose homeostasis, suppressed activities of glycolytic enzymes, pyruvate dehydrogenase, citric acid cycle enzymes, and mitochondrial respiratory chain complexes I–IV. Western blotting showed that MS suppressed phosphorylated PI3K, AKT, and mTOR, increased PTEN expression, and reduced Rheb levels, indicating impaired PI3K/AKT/mTOR signaling. Fasudil treatment normalized plasma and hippocampal glucose levels, restored enzyme activities across glycolysis, the citric acid cycle, the respiratory chain, and reactivated the PI3K/AKT/mTOR pathway by reducing PTEN and restoring AKT and Rheb activity. These molecular changes were accompanied by improvements in hippocampal metabolic function, suggesting effective restoration of neuronal energy homeostasis.

Importantly, our findings indicate that ROCK overactivation is a mechanistic contributor to central insulin resistance and hippocampal energy deficits in MS. Pharmacological ROCK inhibition with fasudil effectively reverses these pathological alterations, highlighting ROCK as a promising target for interventions aimed at restoring neuronal metabolic function and supporting hippocampal resilience in metabolic syndrome.