Fenolni spojevi promiču translokaciju prijenosnika glukoze 4 (GLUT4) i poboljšavaju potrošnju glukoze u tkivima

Voditelj projekta

prof. dr. sc. Jasminka Giacometti

Sveučilište u Rijeci, Odjel za biotehnologiju
e-mail: jgiacometti@uniri.hr

Suradnici

prof. dr. sc. Damir Muhvić dr. med., Sveučilište u Rijeci, Medicinski fakultet
doc. dr. sc. Tanja Grubić Kezele dr. med., Sveučilište u Rijeci, Medicinski fakultet
izv. prof. dr. sc. Marina Nikolić dr. med., Sveučilište u Rijeci, Medicinski fakultet
izv. prof. dr. sc. Tamara Šoić-Vranić dr. med, Sveučilište u Rijeci, Medicinski fakultet
mr. sc. Ariana Fužinac-Smojver dr. med., Sveučilište u Rijeci, Fakultet zdravstvenih studija

Sažetak

Glukoza je primarni izvor energije za većinu stanica i važan supstrat mnogih biokemijskih reakcija. Ulazak glukoze u stanice postiže se aktivacijom fosforilacije glukokinaze i posredovanjem niza prijenosnika glukoze (GLUT) koji se međusobno razlikuju prema specifičnosti, raspodjeli i mehanizmu regulacije. Inzulin stimulira translokaciju prijenosnika glukoze 4 (GLUT4) koji se vezikularnim putem transportira na staničnu membranu (SM) aktivacijom signalnog puta fosfatidilinozitol 3-kinaza/aktin (PI3K/Akt) i Cb1-CAP-CrkII- C3G-TC10 puta.

Aktivacija PI3K puta nije dovoljna za translokaciju GLUT4, već je potrebno dodatno aktivirati put TC10.

Inzulinsko signaliziranje utječe na strukturne i dinamičke elemente uključene u mobilizaciju, vezanje i spajanje GLUT4 vezikula na SM. Rab GTP-aze sudjeluje u formiranju GLUT vezikula, utječu na njezinu pokretljivost/isporuku duž citoskeleta i spajanje/vezanje na SM, dok SNARE proteini omogućavaju spajanje GLUT4 na SM.

Mehanizam kojim inzulin regulira potrošnju glukoze u perifernim tkivima još uvijek nije u potpunosti poznat, posebice kad se radi o unosu lijekova i prirodnih spojeva s hipoglikemijskim učinkom kao što su bioaktivni fenolni spojevi. S druge strane, poremećena homeostaza glukoze u inzulinskoj rezistenciji je rezultat deregulacije signalnih putova PI3K/Akt, mitogen-aktivirane protein kinaze (MAPK) i AMP-aktivirane protein kinaze (AMPK). Oštećene funkcije Rab i SNARE proteina izravno utječu na translokaciju GLUT4 i spajanje na SM.

Bioaktivni fenolni spojevi mogu stimulirati unos glukoze induciranjem ekspresije GLUT4, utjecati na translokaciju GLUT4 i vezanje na SM. To je do sada potvrđeno u istraživanjima učinaka resveratrola, klorogene, galne, ferulične i elagične kiseline te karnozola na *in vitro* modelima.

Ovaj projekt će istražiti poboljšanje potrošnje glukoze putem ključnih elemenata translokacije GLUT4 u inzulin-osjetljivim i inzulin-neosjetljivim tkivima u održavanju homeostaze glukoze *in vivo*.

Phenolic compounds promote glucose transporter 4 (GLUT4) and improve glucose uptake in tissues

Principal investigator

Prof. Jasminka Giacometti, Full Prof., tenure

University of Rijeka, Department of Biotechnology
e-mail: jgiacometti@uniri.hr,

Team members

Prof. Damir Muhvić, MD, Full Prof., tenure, University of Rijeka, Faculty of Medicine
Assist. Prof. Tanja Grubić Kezele, MD, University of Rijeka, Faculty of Medicine
Assoc. Prof. Marina Nikolić, MD, University of Rijeka, Faculty of Medicine
Assoc. Prof. Tamara Šoić-Vranić, MD, University of Rijeka, Faculty of Medicine
M.Sc. Ariana Fužinac-Smojver, MD, University of Rijeka, Faculty of Health Studies

Abstract

Glucose is the primary source of energy for most cells and an important substrate of many biochemical reactions. The entry of glucose into cells is achieved by the activation of glucokinase phosphorylation and the mediation of a series of glucose transporters (GLUTs) that differ in each other according to the specificity, distribution and mechanism of regulation. Insulin stimulates the translocation of glucose transporter 4 (GLUT4) vesicles to the plasma membrane (PM) by the activation of the signal pathway of phosphatidylinositol 3-kinase/actin (PI3K/Akt) and Cb1-CAP-CrkII-C3G-TC10 pathway.

Activation of the PI3K time is not sufficient for the GLUT4 translocation, so the TC10 need to be further activated.

Insulin signaling affects the structural and dynamic elements involved through the intracellular localization, mobilization, tethering, docking and fusion of GLUT4 vesicles with the PM. Rab GTPases participates in the formation of GLUT vesicles, affects its mobility/delivery along the cytoskeleton and tethering/fusion with the PM. SNARE proteins and several regulatory factors mediate this process.

The mechanism by which insulin regulates glucose uptake in peripheral tissues is still not fully clarifying, particularly in case of intake of drugs and natural compounds with hypoglycemic effects such as bioactive phenolic compounds. In addition, the impaired glucose homeostasis in insulin resistance is the result of deregulation of signal pathways PI3K/Akt, mitogen-activated protein kinase (MAPK) and AMP-activated protein kinase (AMPK). Damaged functions of Rab proteins and SNARE proteins directly affect GLUT4 translocation and fusion with the PM.

Bioactive phenolic compounds can stimulate glucose uptake by inducing GLUT4 expression, affecting on GLUT4 translocation and fusion to PM. This has so far been confirmed in the studies applied resveratrol, chlorogenic, gallic, ferulic and ellagic acids and carnosol on *in vitro* models.

This project aims to investigate the improvement of glucose uptake in insulin-sensitive and insulin-insensitive tissues through the GLUT4 translocation elements to maintain glucose homeostasis *in vivo*.