

차세대 당뇨병 치료제 표적물질 발굴

- 주저자 : 박창균, 김승일
- 교신저자 : 김건화(생명과학)
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연구내용

간에서 해독 작용에 관여 하는 막단백질인 CYP4A (Cytochrome P450 4A)의 활성을 억제함으로써 제 2형 당뇨병의 치료에 효과가 있음을 규명. 단백질체 분석을 통해 제2형 당뇨병이 유발된 생쥐의 간에서 정상 쥐에 비해 CYP4A 막 단백질이 과다 발현되어 있음을 확인하였으며, CYP4A 막 단백질의 발현 및 기능을 조절함으로써 제2형 당뇨병을 치료할 수 있다는 가능성을 확인함.

※ CYP4A는 간의 해독작용과 약물대사에 관여하는 대표적인 막 단백질로 특히 생리활성 지질 분자를 형성하는데 중요한 역할을 수행하는 것으로 알려져 있음.

이에 따라 연구팀은 식욕조절 호르몬 유전자 조작에 의해 당뇨병이 유발된 생쥐의 간에서 CYP4A 막 단백질의 발현을 억제시킨 결과 공복 혈당을 비롯한 당뇨병 관련 증상들이 개선된 것을 확인하고, 또한 유전자 조작 또는 고지방식 섭취로 비만과 당뇨가 유발된 생쥐 모두에게 CYP4A 막 단백질의 활성을 저해하는 치료후보물질을 투여한 결과 양쪽 모두에서 몸무게가 감소하고 지방간과 당뇨병 증상이 정상적으로 회복되었다고 밝힘.

이번 연구결과는 간의 해독작용에 관여하는 막 단백질이 비만 등에 의해 과다 발현되면, 간세포에 소포체 스트레스가 발생하여 간이 정상적인 기능을 잃게 되어 당뇨병이 유발된다는 새로운 당뇨병 유발 기전을 최초로 규명하였고, 이를 통해 차세대 당뇨병 치료제 개발을 위한 표적 단백질을 발굴했다는 점에서 큰 의미가 있음.

기대효과

사람 몸의 생명활동 과정에서 나타나는 각종 독소를 해독하는 역할을 하는 간(liver)에서 그 해독작용과 직접 관련된 단백질의 활성을 조절하는 것만으로 당뇨병이 개선되는 효과를 밝혀냄에 따라 새로운 당뇨병 치료제 개발의 길이 열리게됨. 부작용이 없는 새로운 당뇨병 치료제 후보물질을 제시 했다는 점에서 큰 의의가 있으며, 최근 기초지원원이 구축한 국내 최고사양의 '하이컨텐츠 스크리닝(HCS) 자동화 장비'를 활용한 후속연구를 통해 제2형 당뇨병 치료를 위한 신약개발로 이어갈 계획임.

Inhibition of CYP4A Reduces Hepatic Endoplasmic Reticulum Stress and Features of Diabetes in Mice

Edmond Changkyun Park,^{1*} Seung Il Kim,^{1*} Yoonhee Hong,¹ Jeong Won Hwang,¹ Gun-Sik Cho,² Hye-Na Cha,² Jin-Kwan Han,² Chul-Ho Yun,³ So-Young Park,⁴ Ik-Soon Jang,⁵ Zee-Won Lee,⁶ Jong-Soon Cho,^{1,5} Soohyun Kim,² and Gun-Hwa Kim^{1,7}

¹Division of Life Science, Korea Basic Science Institute, Guseong, Republic of Korea; ²Division of Molecular and Life Sciences, Pohang University of Science and Technology, Pohang, Gyeongbuk, Republic of Korea; ³Department of Physiology, College of Medicine, Yonsei University, Incheon, Republic of Korea; ⁴School of Biological Sciences and Technology, Chonnam National University, Gwangju, Republic of Korea; ⁵School of Analytical Science and Technology, Chonnam National University, Gwangju, Republic of Korea; ⁶Institute of Biomedical Science, Republic of Korea; ⁷Department of Functional Genomics, University of Science and Technology, Daejeon, Republic of Korea

BACKGROUND & AIMS: Endoplasmic reticulum (ER) stress is implicated in the development of type 2 diabetes mellitus. ER stress activates the unfolded protein response pathway, which contributes to apoptosis and insulin resistance. We investigated the role of cytochrome P450 4A (CYP4A) in the regulation of hepatic ER stress, insulin resistance and the development of diabetes in mice. **METHODS:** We used mice specifically to suppress levels of CYP4A proteins in livers from C57BL/6J and C57BL/6Jdb/db (db/db) mice; findings were confirmed by immunoblot and real-time PCR analyses. To create a model of diet-induced diabetes, C57BL/6J mice were placed on high-fat diets. Mice were given intraperitoneal injections of an inhibitor (GW401166) or an inducer (dithioerythritol) of CYP4A, or tail injections of small hairpin RNAs against CYP4A messenger RNA; liver tissues were collected and analyzed for ER stress, insulin resistance, and apoptosis. The effect of GW401166 and CYP4A knockdown also were analyzed in HFD-fed mice. **RESULTS:** Levels of the CYP4A isoforms were tightly up-regulated in livers of db/db mice compared with C57BL/6J mice; inhibition of CYP4A in db/db and mice on high-fat diets reduced features of diabetes such as insulin hypersecretion, hepatic resistance, and increased glucose tolerance. CYP4A inhibition reduced levels of ER stress, insulin resistance, and apoptosis in livers of db/db mice. It also restored hepatic functions. Inversely, induction of CYP4A accelerated ER stress, insulin resistance, and apoptosis in livers of db/db mice. **CONCLUSIONS:** CYP4A protein is up-regulated in livers of mice with genetically induced and diet-induced diabetes; inhibition of CYP4A in mice reduces hepatic ER stress, apoptosis, insulin resistance and steatosis. Strategies to reduce levels or activity of CYP4A proteins may be developed for treatment of patients with type 2 diabetes.

Keywords: Mouse Model; Obesity; UPR; Proteomic Analysis.

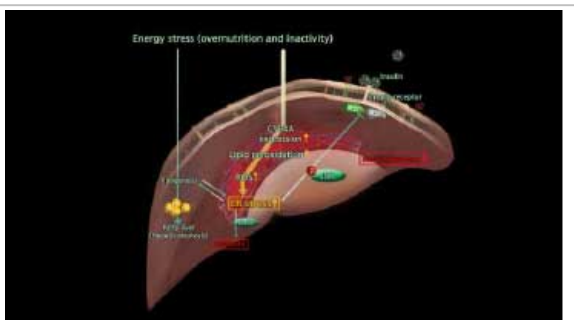
most prevalent and serious metabolic disease in the world, affecting 0.9% (205 million) of the global population and accounting for more than 90% of diabetic patients.^{1,2} Therefore, extensive studies of the developmental mechanisms underlying T2DM, as well as effective treatments, are needed urgently to curtail this epidemic. Obesity is a major pathology underlying the development of insulin resistance, nonalcoholic fatty liver disease, and nonalcoholic disease. Endoplasmic reticulum (ER) stress, which can be induced by obesity and/or metabolic stress, has been proposed as a novel mechanism for the development of insulin resistance in obese individuals.^{3,4} ER stress is caused by disruption of Ca²⁺ homeostasis, overload of protein/lipid biosynthesis, and oxidative stress, which trigger the evolutionarily conserved complex homeostatic signaling pathway known as the unfolded protein response (UPR). Translocation of UPR signaling is performed by 3 ER transmembrane proteins: inositol-requiring enzyme 1 (IRE1), activating transcription factor 1 (ATF6), and protein kinase double-stranded RNA-dependent-like ER kinase (PERK).⁵ Activation of UPR signaling leads to transcriptional activation of ER chaperones and reduced protein synthesis, which aid in the re-establishment of homeostasis of ER

*Authors share co-first authorship.

Abbreviations used in this paper: ATF6, activating transcription factor 6; ER, endoplasmic reticulum; IRE1, inositol-requiring enzyme 1; PERK, protein kinase double-stranded RNA-dependent-like ER kinase; UPR, unfolded protein response; CYP4A, cytochrome P450 4A; db/db, mice with genetically induced diabetes; HFD, high-fat diet; HFD-fed mice, mice fed with high-fat diet; HFD-induced diabetes, mice with diet-induced diabetes; IRE1, inositol-requiring enzyme 1; JNK, c-Jun N-terminal kinase; NADPH, nicotinamide adenine dinucleotide; NADPH oxidase; PERK, protein kinase double-stranded RNA-dependent-like ER kinase; PGC-1 α , peroxisome proliferator-activated receptor- γ coactivator 1; PKR, cytokine-inducible shutoff of apoptosis; RER, rough endoplasmic reticulum; RER-derived ER stress; UPR, unfolded protein response; UPR, unfolded protein response; UPR1, inositol-requiring enzyme 1.

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[그림 1] 작용기작 모델 그림

[그림 2] 관련 논문