論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	謝　可宇 (XIE KEYU)
論文題名 Title	Effects of luseogliflozin treatment on hyperglycemia-induced muscle atrophy in rats (高血糖誘発性筋萎縮モデルにおけるルセオグリフロジンの効果)

論文内容の要旨

〔目　的(Purpose)〕

The prevalence of lifestyle-related diseases, such as diabetes mellitus, is increasing. Many reports show that there is an association between diabetes and sarcopenia. It has been suggested that hyperglycemia induces degradation of muscle protein. Therefore, it is important to prevent hyperglycemia-associated muscle atrophy to extend healthy life expectancy in patients with diabetes. Luseogliflozin, a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, reduces inflammation and oxidative stress by improving hyperglycemia, subsequently improving hepatosteatosis or kidney dysfunction. However, the effects of SGLT2 inhibitor on the regulation of skeletal muscle mass or function in hyperglycemia are still unknown. In this study, we investigated the effects of luseogliflozin-mediated attenuation of hyperglycemia on the prevention of muscle atrophy.

〔方法(Methods)〕

The animals were randomly divided into four groups: control (Control group), control with SGLT2 inhibitor treatment (SGLT2i group), hyperglycemia without SGLT2 inhibitor treatment (STZ group), and hyperglycemia with luseogliflozin treatment groups (STZ+SGLT2i). Hyperglycemic models were established by a single intraperitoneal injection of streptozotocin (STZ, 40mg/kg). After 5 weeks' hyperglycemic induction, the Sprague-Dawley rats were fed standard diet (Control group, STZ group) or a selective sodium-glucose cotransporter 2, luseogliflozin administrated by mixing into their diet at the concentration of 0.01% (SGLT2i group, STZ+SGLT2i group). After 4 weeks, lower limb skeletal muscles and liver were collected, Histological sections were made. Protein extraction and RNA extraction were performed.

〔成績(Results)〕

Hyperglycemia rats exhibited decrease of cross-sectional area, increases in blood glucose levels, liver wet weight, advanced glycation end products (AGEs) and increases in the expression of mitochondrial and ubiquitin-proteasome pathway genes. SGLT2 inhibitor luseogliflozin halved the blood glucose level, decreased the liver wet weight, prevent the decrease of cross-sectional area in the situation of hyperglycemia and partially attenuated increased muscle protein degradation through the activation of ubiquitin-proteasome pathway caused by hyperglycemia, the increase in advanced glycation end products accumulation resulting from hyperglycemia and the increase in superoxide dismutase 2 (SOD2) expression owing to the modulation of the compensation effect related to STZ-induced hyperglycemia. Protein expression levels of mitochondrial respiratory chain complexes III and IV were significantly higher in the STZ group than those in the Control group, and in STZ+SGLT2 inhibitor were similar to those in Control group.

〔総　括(Conclusion)〕

Treatment with luseogliflozin can restore the hyperglycemia-induced muscle mass loss to some degree partly through the inhibition of AGEs-induced or homeostatic disruption of mitochondria-induced activation of muscle degradation. We only partially identified the mechanism by which this occurred in this study. More research is needed to clarify the complete mechanism.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

申請者は、高血糖モデルラットを用いて、糖尿病治療薬であるSodium-glucose cotransporter 2(SGLT2)阻害剤がサルコペニアを予防できる可能性について研究を行った。これまでに多くの報告で、糖尿病とサルコペニアの間に関連があるといわれており、その機序として高血糖が筋タンパク質の分解を誘発すると考えられている。高血糖に伴う筋萎縮を予防することは、糖尿病患者の健康寿命の延伸に重要である。しかし、SGLT2阻害薬によって高血糖を改善することが、骨格筋の萎縮の軽減につながるかどうかは明らかになっておらず、申請者はこの点についての研究を行った。

高血糖モデルラットとして、ストレプトゾトシン(STZ)を投与したラットを用いた。このモデルにSGLT2阻害薬を投与することにより、血糖、体重、骨格筋（特に前脛骨筋）の横断面積を検討した。高血糖モデルラットにSGLT2阻害薬を投与することにより、血糖は低下し、骨格筋の横断面積の減少が改善し、終末糖化産物(Advanced glycation end products: AGEs)の蓄積が軽減され、筋タンパク質分解マーカーの増加が抑制され、さらに酸化ストレス恒常性の破綻が抑制されることが明らかになった。したがって、SGLT2阻害薬は高血糖の抑制にとどまらない様々な機序を介して、サルコペニア予防に働く可能性が考えられた。

本論文審査により、申請者は学位の授与に値すると考えられる。