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様式１０２

学位論文の内容の要旨

専　攻	医学	部　門 (平成27年度以前入学者のみ記入)	
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論文題目	Luseogliflozin, a SGLT2 Inhibitor, Does Not Affect Glucose Uptake Kinetics in Renal Proximal Tubules of Live Mice		

（論文要旨）

Sodium-glucose cotransporter 2 (SGLT2), expressed on brush border membranes, transports sodium and glucose from the tubular lumen into the cells. It is believed that glucose taken up through SGLT2 flows across the cells and is transported to the interstitium. Glucose transporter 2 (GLUT2), expressed in the basement membrane, transports glucose from the intracellular space to interstitial fluid. GLUT2, on another hand, is known as a facilitating bidirectional glucose transport in the liver. In our previous study using intravital imaging at a subcellular spatial resolution, we found that GLUT2 downregulation dramatically reduced cellular glucose uptake into the proximal tubules of mice treated with luseogliflozin, a SGLT2 inhibitor. This observation suggested the potential for glucose uptake by GLUT2 in the kidney under the influence of SGLT2 inhibitors. This prompted our interest in determining whether SGLT2 inhibition using luseogliflozin affects glucose uptake dynamics in the proximal tubule cells of live mice. We evaluated glucose uptake dynamics with and without luseogliflozin under different levels of blood glucose using a fluorescent glucose analogs 2-deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]-D-glucose (2-NBDG) in vivo and 2-deoxyglucose in vitro to visualize glucose dynamics.

Mice were divided into 6 groups: hypoglycemia + vehicle, normoglycemia + vehicle, hyperglycemia + vehicle, hypoglycemia + luseogliflozin(0.9 mg/kg, i.p.), normoglycemia + luseogliflozin and hyperglycemia + luseogliflozin groups. We used 2NBDG to observe the dynamics of glucose in tissues of live mice under multi-photon microscopy. After administering 2-NBDG through the jugular vein, peak fluorescence, time to achieve at peak level(Tmax), and peak/Tmax were analyzed separately in the three groups according to blood glucose level. The reliability of our in vivo imaging system was confirmed by measuring the insulin-accelerated 2-NBDG uptake in skeletal muscle. In animal study, Luseogliflozin did not significantly affect blood glucose level in the either hypo- or normoglycemia groups. In the streptozotocin (STZ)-induced hyperglycemia group, luseogliflozin decreased blood glucose levels. In the kidney proximal tubules, luseogliflozin did not significantly affect peak, Tmax and peak/Tmax in all groups. Blood glucose level did not significantly affect basolateral glucose transport in proximal tubules .In addition, GLUT2 protein levels were similar in all groups. Cell study showed that luseogliflozin did not affect glucose uptake through GLUT. These data suggested that treatment with luseogliflozin did not cause changes in glucose uptake kinetics in the proximal convoluted tubules of the kidney in normal mice.

In conclusion, treatment with luseogliflozin did not cause changes in glucose uptake kinetics in the proximal convoluted tubules of the kidney in normal mice. Bidirectional transport of GLUT2 may be the main factor why the proximal convoluted tubule maintains similar glucose uptake kinetics following luseogliflozin treatment.

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