Comment on: Gorboulev et al. Na^+-D-glucose Cotransporter SGLT1 Is Pivotal for Intestinal Glucose Absorption and Glucose-Dependent Incretin Secretion. Diabetes 2012;61:187–196

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The elegant paper from Koepsell and colleagues (1) demonstrates the apical GLUT2 mechanism, but appears at first sight to question its significance. However, when set in a physiological context, the results are those expected from the three roles of SGLT1 and the differences between fed rat and starved mouse.

SGLT1 acts as *1*) a transporter and *2*) a powerful scavenger. In 2000, my laboratory proposed that SGLT1 also has *3*) a pivotal regulatory role, controlling the rapid insertion and activation of GLUT2 at the enterocyte apical membrane so that absorptive capacity matches glucose load.

When rodents are fed a high carbohydrate diet or food is flushed from the gut immediately before transport studies, then, at high glucose concentrations, transport through SGLT1 increases apical GLUT2 and intrinsic activity within minutes. When glucose is plentiful, therefore, GLUT2 is a major pathway of absorption, accounting for ~75% in rats and ~50% in mice, where SGLT1 is exceptionally high. This proposal was confirmed in GLUT2 knockout mice by Brot-Laroche and colleagues (2) and described by many laboratories. A vivid demonstration of SGLT1/apical GLUT2 regulation is seen in phase 3 (protein catabolism) starvation in rats (3), where SGLT1 increases threefold and apical GLUT2 becomes undetectable. On refeeding, high carbohydrate returns SGLT1 to control values, and massive amounts of GLUT2 appear at the apical membrane within 2 h.

In the study by Gorboulev et al. (1), mice were starved overnight before transport studies. In starvation, if some GLUT2 were to remain at the apical membrane, transport of glucose from plasma to lumen would occur through GLUT2 down the concentration gradient; Na^+ transported by SGLT1 is also secreted into the lumen by claudin-15 to maintain SGLT1 activity (4). To prevent loss of glucose and Na^+ from the body, it is vital they be reabsorbed by scavenging; SGLT1 is therefore strongly upregulated, and apical GLUT2 downregulated. Their study demonstrates perfectly that regulation during overnight starvation in mouse is similar to phase 3 starvation in rat, but not quite as extreme.

In conclusion, we agree that SGLT1 is pivotal in intestinal glucose absorption. Indeed, we have gone further than the classical view by emphasizing in every article that the significance of SGLT1 is enhanced by its role in regulating apical GLUT2.

ADDENDUM

Mace et al. have since reported that incretin secretion is regulated by both SGLT1 and apical GLUT2 in rats fed a high carbohydrate diet. See Mace OJ, Schindler M, Patel S. The regulation of K- and L-cell activity by GLUT2 and CasR in rat small intestine. J Physiol. 10 April 2012 [Epub ahead of print]

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