Stress and intestinal sugar absorption

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TWENTY YEARS AGO, Ugolev et al. (15) noted that “under physiological conditions [the] two systems of glucose transport, Na+-dependent and Na+-independent, function. The first one is less potent but more resistant to experimental influences.” This statement sums up fairly accurately what has happened in the field of intestinal sugar absorption in the last six years as exemplified by increases in our understanding of the way in which a wide range of stimuli regulate the two components of sugar absorption mediated by the Na+-glucose cotransporter SGLT1 and apical GLUT2 (12). The article by Baudry et al. (2) in this issue of AJP–Regulatory, Integrative and Comparative Physiology reports how both components are regulated in opposite directions by psychological stress and contrasts with the mechanism by which environmental stress regulates only apical GLUT2 (14).

In 2000, my laboratory advanced a new explanation for the diffusive (Na+-independent) component of glucose absorption (8, 9, 13). We observed that when rat jejunum is perfused in vivo with concentrations of glucose greater than that required to saturate SGLT1, the facilitative transporter GLUT2 is inserted into the apical membrane within minutes, although it is normally present predominantly in the basolateral membrane at lower concentrations. Since GLUT2 is a high Km, high-capacity transporter (3) compared with SGLT1, GLUT2 can provide a diffusive or facilitated component several times greater than the active component at high glucose concentrations. Apical GLUT2 therefore provides a cooperative mechanism by which absorptive capacity is rapidly and precisely matched to dietary intake. However, when SGLT1 activity is blocked with phloridzin, apical GLUT2 insertion is prevented (13). Thus SGLT1 and apical GLUT2 work in concert to cover the necessary physiological concentration range from low to high dietary glucose; moreover, SGLT1 exerts a powerful regulatory role over apical GLUT2 (11). The apical GLUT2 model has been confirmed by studies in GLUT2 null mice (5); moreover, apical GLUT2 is regulated by a wide range of physiological stimuli including, long- and short-term dietary sugars (5), local hormones, such as GLP2 (1), perfusion rate (7), cellular energy status (16), starvation (6), and diabetes (4) (for a review, see Ref. 12).

Baudry et al. (2) have now reported the regulation of sugar absorption by water avoidance stress (WAS), a chronic form of psychological stress. Working with Brown Norway background rats, which have been characterized with respect to WAS in some detail, they first studied 3-O-methylglucose absorption in stripped mucosa in Ussing chambers; in this preparation, transport is almost exclusively by SGLT1, because GLUT2 rapidly traffics away from the membrane at low sugar concentrations in vitro (9). Vmax determined by short-circuit current was halved after 1, 5, or 10 days of WAS and Km was also reduced significantly. Since there was no change in SGLT1 abundance in Western blot analysis, the changes were attributed to alterations in Na+-K+-ATPase activity.

GLUT2 transports both glucose and fructose, so that fructose absorption across the apical membrane is mediated not only by GLUT5 but also by GLUT2 (5, 9); moreover, only GLUT2 is sensitive to phloretin. If care is taken to block GLUT2 trafficking in vivo at the start of brush-border membrane vesicle preparation, then measurements of phloretin-sensitive fructose uptake provide a clear-cut way in which to assess what is happening to apical GLUT2 independently of SGLT1. Baudry et al. (2) found that after 10 days of WAS, GLUT2-mediated fructose transport was severalfold greater than for control animals and correlated with a large increase in apical GLUT2.

This remarkable reciprocal regulation of SGLT1 and apical GLUT2 is reminiscent of what happens when the energy status of cells is under stress as demand for energy exceeds supply. In this case, AMP-activated protein kinase (AMPK) is activated as the AMP-to-ATP ratio increases so that apical GLUT2 insertion is increased as total cellular SGLT1 is degraded within 30 to 60 min (16). Thus the dependence of apical GLUT2 on SGLT1 is overridden as the energy-requiring transport system is switched off and the energy-independent system is switched on.

Interestingly, the mechanism by which WAS regulates sugar absorption is quite different from that for environmental stress reported by Shepherd et al. (14). These authors undertook an opportunistic study when construction activity during the expansion of their department resulted in large changes in absorption in Wistar rats. Although there was no change in the SGLT1 component or abundance, there was a 42% decrease in the apical GLUT2 component and insertion. The decrease in absorption could be mimicked by dexamethasone injection into unstressed rats just 1 h before perfusion. In this respect, the mechanism is analogous to the blocking of insulin-induced GLUT4 translocation in muscle by dexamethasone (10).

Modeling of chronic stress is difficult, and the differences in mechanism may well reflect a combination of different animal strains and stress stimuli. Compared with WAS, environmental stress was mild, being intermittent and poorly-defined; moreover, it did not cause any decrease in food intake or change in water transport, which are classic hallmarks of psychological stress. Both types of stress induce a general catabolic state with inevitable implications for the regulation of the HPA axis and the recycling of metabolites. The WAS study is the first report of a properly defined stress stimulus on intestinal sugar absorption; it is therefore very helpful to readers that there is a lucid description of stress both in general terms and more specifically with respect to intestine and nutrient absorption. There is much work to do on the intracellular signaling mechanisms. The future of research on intestinal function is regulation.
REFERENCES


