SIGNIFICANCE STATEMENT

The facilitative glucose transporter GLUT2, localized in the proximal tubule, is recruited to the apical/brush border membrane (BBM) during hyperglycemia, contributing to increased glucose reabsorption and potentially, inflammatory injury and tubulointerstitial fibrosis. Activating cannabinoid-1 receptor (CB_1R) also triggers these abnormalities, but the link between CB_1R and GLUT2 has been poorly defined. This manuscript deciphers the signaling pathway involved in regulating GLUT2 expression/translocation to the BBM *via* the CB_1R by using pharmacologic blockade and by genetic deletion of CB_1R in proximal cells. Our findings contribute to the rationale for clinical testing of peripherally restricted CB_1R antagonists or developing novel renal-specific GLUT2 inhibitors against DN.