Fexofenadine (FEX), a second generation H1-receptor antagonist, is mainly eliminated from the liver into bile in its unchanged form. Recent studies have shown that FEX is a substrate of MDR1 (P-gp), OATP-A and OATP-B in humans. However, transporters responsible for the hepatic uptake of FEX and their clinical relevance have not yet been determined. In the present study, we evaluated the contribution of OATP2 (OATP-C/OATP1B1) and OATP8 (OATP1B3) to FEX uptake using transporter-expressing HEK293 cells. The uptake of FEX in OATP8-expressing cells was significantly greater than that in vector-transfected cells (P < 0.05). On the other hand, OATP2-mediated uptake of FEX was not statistically significant. OATP8-mediated transport could be explained by a one-saturable component with the Michaelis constant (Km) of 108 µM. The inhibitory effect of FEX on the uptake of estrone-3-sulfate (E-sul) (for OATP2) and cholecystokinin octapeptide (CCK-8) (for OATP8) was also examined. In the presence of 100µM FEX, OATP2-mediated uptake of E-sul was not significantly inhibited, while OATP8-mediated CCK-8 uptake was decreased to 50% of control (P < 0.05), suggesting that the inhibitory effect of FEX on the uptake via OATP8 was greater than that on the uptake via OATP2. This is the first demonstration that FEX is the substrate for OATP8 and FEX may interact preferentially with OATP8 rather than OATP2 in this transporter-expressing cell line. We are now investigating the quantitative contribution of OATP2 and OATP8 to the hepatic uptake of FEX using transfectants and human hepatocytes.