According to the neurovascular hypothesis, impaired clearance of the amyloid-beta (Aβ) peptide across the blood-brain barrier (BBB) contributes to Alzheimer's disease (AD) pathology. However, conflicting findings on the involvement of different Aβ transporters at the BBB and their expression in brain endothelium have questioned the role of LRP1 and Pgp at the BBB. As global knockout of Lrp1 in mice is lethal, there is a lack of appropriate models to study the function of LRP1. Moreover, the relevance of systemic Aβ clearance remains unclear as no BBB-specific knockout models had been available. We used in vitro and in vivo methods to quantify the rate of Aβ clearance across the BBB. With a novel Slco1c1-CreERT2 mouse, we generated the first brain endothelial-specific Lrp1 knockout mouse to accurately evaluate LRP1-mediated Aβ BBB-clearance in vivo. Using stereotactical injections of physiological concentrations of radiolabeled Aβ peptides, we were able to quantify the rate of LRP1 mediated clearance at the BBB in vivo. Crossing the LRP1 KO mice to the 5xFAD mouse model resulted in reduced plasma Aβ and elevated soluble brain Aβ leading to aggravated spatial learning and memory deficits, thus, emphasizing the importance of systemic Aβ elimination via the BBB. By combining primary mouse brain endothelial cells from these animals with Pgp inhibitors, we are able to identify the role of each transporter at the BBB for Aβ clearance in vitro. Dissecting the function of these transporters may provide new approaches for treatment and prevention of Aβ brain accumulation in AD.