Nucleotides are released from cells in response to tissue damage and activate P2X and P2Y receptors on the cell surface to regulate inflammation, a critical process in response to injury. During inflammation, white blood cells/leukocytes are recruited from the bone marrow (BM) to the bloodstream and cross the vasculature at sites of injury or infection. Accumulating evidence indicates that the P2Y₂ nucleotide receptor (P2Y₂R) is an important regulator for many inflammatory events, especially vascular barrier function and leukocyte enrichment in the affected tissue. Here, we show that the endothelial P2Y₂R in the blood vessels contributes to the transmigration of leukocytes and large molecules through blood vessels by loosening the cell-cell junctions and activating signaling pathways that disrupt the vascular barrier integrity. Studies in the TgCRND8 (Tg⁺) mouse model of Alzheimer’s disease, a chronic inflammatory and neurodegenerative disease, demonstrate that the P2Y₂R regulates the release of two types of leukocytes, neutrophils and monocytes, from the BM to the peripheral blood, which may contribute to clearance of toxic β-amyloid plaques in the brain, the major cause of the disease. The impaired leukocyte emigration out of the BM in Tg⁺ mice lacking sufficient P2Y₂R is likely due to the essential role of the P2Y₂R in leukocyte migration while the retention signals for blood cells in the BM is strikingly reduced compared to Tg⁺ mice. In summary, this work has revealed novel functions of the P2Y₂R in regulation of leukocyte trafficking from the BM to the blood and to inflammatory sites during inflammation.