The effects of ambrisentan, a selective endothelin ET_A receptor antagonist for vasogenic edema after traumatic brain injury in mice

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Vasogenic edema is a severe condition resulted from disruption of blood-brain barrier (BBB) after traumatic brain injury (TBI). Endothelin (ET) is an aggravating factor for the BBB disruption. In this study, we confirmed the effects of ambrisentan, an ETA receptor antagonist for TBI-induced vasogenic edema. As a model of TBI, mice (male ddY, 6 to 7 weeks) were given fluid percussion injury (FPI) by hydraulic impact on dura mater. Ambrisentan (0.02, 0.1 and 0.5 mg/kg/day) were repeatedly administrated from mouse tail vein in 6 hour to 2 days after FPI. To evaluate vasogenic edema, the BBB disruption and brain edema were evaluated by Evans blue extravasation and brain water content, respectively. Expressions of vascular endothelial growth factor-A (VEGF-A) as an aggravating factor for the BBB disruption and angiopoietin-1 (ANG-1) as a protective factor were measured by Real-time PCR. Expression of ETA receptors was observed by immunohistochemistry. The i.v. administrations of ambrisentan ameliorated the BBB disruption and decreased in brain water content in 2 day after FPI. Ambrisentan decreased in VEGF-A and increased in ANG-1 after FPI. The immunochemical observations indicated that ETA receptors were distributed in brain endothelial cells in mouse cerebrum. In vitro experiments, treatment with ET-1 (100 nM) increased in VEGF-A and decreased in ANG-1 in brain endothelial cells (bEnd.3 cells). Treatment with ambrisentan (1 μM) inhibited the effects of ET-1. These results suggest that ambrisentan is expected to be a novel therapeutic drug for vasogenic edema.