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The γ-secretase activation induces the permeability of the blood-brain barrier by increasing the ubiquitination and degradation of occludin during brain ischemia

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The ubiquitin-proteasome system is the major pathway for protein degradation in the cytoplasm of eukaryotic cells, yet there have been few studies describing this system in the microvessels of the brain. We here studied the effect of γ-secretase inhibitor on occludin degradation after permanent middle cerebral artery occlusion (pMCAO) in rats. Consistent with ZO-1 degradation as indicated by the decrease of 220 kDa in 24 h after pMCAO, we observed ubiquitination and degradation of occludin in same context. We further investigated the candidate protease(s) implicated in the degradation of occludin during pMCAO. Notably, the γ-secretase blocker DAPT significantly inhibit pMCAO-induced neurovascular damage, whereas ALLM and Batimastat were less effective. Consistently, present data demonstrated that DAPT significantly inhibited BBB disruption as assessed by Evans blue excretion in comparison with vehicle. Furthermore, the protective effect of DAPT on BBB likely associated with its inhibitory effect on ubiquitination and degradation of occludin, which might be the potential downstream targets of γ-secretase in brain microvessels following ischemia. Overall, we show that inhibition of γ-secretase signaling as well as Itch-mediated ubiquitination of occludin probably underlies the vasoprotective mechanisms of DAPT. The observed protection of occludin protein and BBB integrity by γ-secretase blocker suggests a novel therapeutic strategy against ischemia-induced neurovascular damage.

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