論 文 審 査 の 結 果 の 要 旨

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（論文審査の結果の要旨）

Angiotensin II receptor blockers (ARBs) are widely prescribed for the medication of systemic hypertension and congestive heart failure. It has been reported that ARBs can reduce the risk for the onset of Alzheimer's disease (AD) and have beneficial effects on dementia. Neurotoxic amyloid β-protein (Aβ) is believed to play a causative role in the development of AD. However, whether ARBs regulate Aβ generation remains largely unknown. Here, we studied the effect of ARBs on Aβ generation.

We infected C57BL/6 mouse embryonic fibroblasts (MEFs) with human 695-amino acid amyloid precursor protein (hAPP695) cDNA by a retrovirus-mediated method to generate constant hAPP695 overexpression fibroblasts (APP fibroblasts). And we treated APP fibroblasts separately with telmisartan, losartan, valsartan, olmesartan and candesartan for 72 h to determine the effect of ARBs on Aβ generation. We measured Aβ40 and Aβ42 levels in the conditioned media by sandwich enzyme-linked immunosorbent assay (ELISA) to determine the Aβ levels. To investigate whether telmisartan increase Aβ generation via angiotensin type 1a receptor (AT1a), we isolated *Agtr1a* deficient MEFs from 13.5-day-old embryos of *Agtr1a* deficient mice and infected the MEFs with hAPP695. We treated *Agtr1a* deficient hAPP-expressing MEFs with telmisartan. To explore which pathway telmisartan depends on to increase Aβ generation, we pre-treated APP fibroblasts with pathway inhibitors and then treated with telmisartan.

Results:

1. We found that telmisartan increased Aβ40 and Aβ42 generation markedly, about 6- and 3.2-fold, respectively, compared to the controls, while olmesartan increased Aβ40 generation about 2-fold at the concentration of 5 μM and Aβ42 generation about 3.2-fold at the concentration of 10 μM. However, losartan, valsartan and candesartan did not show any clear increase in the Aβ generation.
2. Among the ARBs examined, telmisartan significantly decreased the Aβ42/Aβ40 ratio and had the lowest Aβ42/Aβ40 ratio, whereas, olmesartan had the highest Aβ42/Aβ40 ratio which was significantly higher than that of telmisartan. Losartan, valsartan and candesartan did not show any clear effect on Aβ42/Aβ40 ratio.
3. We also found that telmisartan did not increase the Aβ40 and Aβ42 generation in the AT1a deficient fibroblasts.
4. Administration of the PI3K pathway inhibitor, wortmannin, and γ-secretase inhibitor, DAPT, markedly blocked the increase Aβ generation by telmisartan.

These results suggest that telmisartan increased the Aβ generation through AT1a and the receptor-related PI3K pathway. Because telmisartan decreased the Aβ42/Aβ40 ratio, which is considered as a causal factor of AD, it is reasonable to deduce the neuroprotective effect of telmisartan. Our findings revealed the different effects of ARBs on Aβ generation and provide new evidence for the relationship between antihypertensive treatment and AD pathogenesis.

主査、副査は一致して本論文を学位論文として価値があるものと認めた。