PT576
Fluvoxamine alleviates ER stress via induction of Sigma-1 receptor.
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Abstract
We have recently demonstrated that induction of sigma 1 receptor (Sig-1R) expression is caused by endoplasmic reticulum (ER) stress through the PERK pathway, which is one of the cell’s responses to ER stress. In addition, it has been demonstrated that cell death signal transmission can be suppressed by up-regulation of Sig-1R. Fluvoxamine (Flx) is a selective serotonin re-uptake inhibitor (SSRI) that is known to have a high affinity for Sig-1R. In the present study, we have shown that treatment of neuroblastoma cells with Flx induces Sig-1R by directly increasing ATF4 translational regulation without any involvement of PERK pathway. The Flx-mediated induction of Sig-1R prevents neuronal cell death by ER stress. Moreover the ER stress resistance by Flx results in reduction of infarction area due to focal cerebral ischemia in mice. This study shows that Flx, frequently used in clinical practice, has the property of alleviating ER stress suggesting that it can be used as a feasible therapy for cerebral diseases caused by ER stress.

PT577
Distribution of Human Umbilical Cord Blood-derived Mesenchymal Stem Cells (hUCB-MSCs) in the Alzheimer’s Disease Transgenic Mouse after a Single Intravenous Injection

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Abstract
Backgrounds: The aim of this study was to track the migration of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) administered via a single intravenous injection and to observe the consequential therapeutic effects in a transgenic Alzheimer’s disease (AD) mouse model.

Methods: 10-month-old APP/PS1 mice received a total injection of 1 x 10^6 cells through the lateral tail vein and were sacrificed 1, 4, and 7 days after administration.

Results: Based upon immunohistochemical analysis, hUCB-MSCs were not detected in the brain for each time point. Instead, most of the injected MSCs were found to be distributed in the lung, heart, and liver. In terms of the molecular effects, statistically
significant differences in the amyloid beta protein, Neprilysin (NEP), and SOX2 levels were not observed among the groups. **Conclusion:** Our study showed that a single dose of 1X10^6 hUCB-MSCs injected intravenously into AD transgenic mice resulted in neither delivery into the brain nor generation of therapeutic benefits via paracrine activity. In order to utilize the intravenous route as an effective delivery route for AD stem cell therapy, it will be crucial to perform additional studies on how to increase the permeability of the BBB and how to decrease the entrapment of cells in organs such as the lung and liver.

**PT578**

Endothelial-monocyte-activating polypeptide-2 (EMAP-2) may be a novel treatment target of Alzheimer’s disease

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**Abstract**

Inflammation has been raised as a candidate of unifying pathogenesis and a target of disease modifying strategy for Alzheimer’s disease (AD). A cytokine, endothelial-monocyte-activating polypeptide-2 (EMAP-2) which amplifies actions of tumor necrosis factor alpha (TNF-alpha), might be an important target, since it is involved in microglial activation and neuronal death. We hypothesize that EMAP-2 is associated with the Alzheimer’s disease, and anti-EMAP-2 antibody could have therapeutic effects on cognitive impairment in amyloid beta-induced AD model animals.

We investigated the association between the EMAP-2 gene, the -9299A/G polymorphism and cognitive impairment in 641 subjects aged from 60 to 80. In addition, we compared EMAP-2 concentration in peripheral blood among people with AD (n = 30), mild cognitive impairment (n = 29), or normal cognition (n = 27). Finally, we examined the effects of anti-EMAP-2 antibody following injecting it to AD model rats on cognitive function using water maze and passive avoidance tests and on a level of cell death in the brain tissue using TUNEL assay.

We found a significant association between the -9299A/G polymorphism (GG vs AG/AA) of EMAP-2 gene and cognitive impairment. GG homozygote compared to A-allele carriers was related to lower mini-mental status examination score (p = 0.001). In addition, EMAP-2 level was significantly higher in the peripheral blood of people with AD than in that of healthy control group (p = 0.05). In the AD model rats, injection of EMAP-2 antibody improved short-term memory (p < 0.01) and fear memory (p < 0.05), and lowered the levels of neuronal cell death in the brain tissue (p < 0.05).

Our results suggested a possible involvement of EMAP-2 in AD pathogenesis, as well as the potential of humanized anti-EMAP-2 antibody as a novel option for AD treatment.

**PT579**

Disease-modifying therapy through enhancement of neuronal Aβ-degrading enzyme neprilysin activity for Alzheimer’s disease

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**Abstract**

Aggregation and deposition of amyloid-β peptide (Aβ) in the brain are triggering events of the long-term pathological cascade of Alzheimer’s disease (AD), and are closely associated with the metabolic balance between Aβ anabolic and catabolic activities. As almost all familial AD mutations cause an increase in the anabolism of a particular form of Aβ, Aβ1-42, leading to Aβ deposition and accelerating AD pathology, a chronic reduction in the catabolic activity would also promote Aβ deposition. Neprilysin is a rate-limiting peptidase involved in brain Aβ catabolism. Mounting evidence that expression levels of neprilysin are decreased in the hippocampus and cerebral cortex of AD patients from the early stages of disease development and also with aging in humans, suggests a close association of neprilysin with the etiology and pathogenesis of AD. Thus, a subtle but long-term decline in neprilysin activity appears to be at least partly responsible for the memory-related symptoms of AD, and up-regulation of neprilysin would be a promising strategy for disease-modifying therapy of AD.

We screened a compound modulating brain neprilysin activity and/or gene expression using a natural product library, and found that catechins, such as ECGc were capable of up-regulating neprilysin via gene expression. However, their bioavailabilities and blood-brain barrier permeability are not always so good, because these compounds are highly hydrophilic. So, we synthesized aliphatic catechin derivatives by introducing an alkyl chain or aliphatic moiety into EGCg to increase Log P values. Interestingly, some of the aliphatic catechin derivatives more strongly up-regulated not only neprilysin but also α-secretase, which acts to preclude Aβ production, than ECGc did. The aliphatic catechins would be promising drug candidates for therapy and prevention of AD. Currently, we are analyzing their in vivo effects on up-regulation of neprilysin.

**PT580**

Alteration of neuronal nitric oxide synthase dimerization contributes to the development of Alzheimer’s disease

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**Abstract**

**Background and purpose:** Although previous studies have suggested that nNOS-derived NO has neuroprotective effects on the development of AD, the underlying molecular mechanisms are not fully elucidated. Here, we investigated whether and how disruption of nNOS dimerization contributes to the development of AD.

**Methods:** Two-month-old hemizygous 5xFAD mice and non-transgenic control, and 6-month-old hemizygous 5xFAD mice and non-transgenic control mice were used in the experiments. A histological investigation for neuronal cell death and CDKS/p35 localization, DHE injection for measurement of ROS increase, LT-PAGE for nNOS dimerization/monomerization, and Western blot for CDKS/p35 expression were performed.