W-1

Overview : Animal Models for Development of Cognitive Enhancers and Action of Drugs

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To gain insight into the etiological mechanism of dementia and to develop clinically effective congnitive enhancers, it is required to prepare animal models with symptoms and mechanism resemble to that in human.

Dementia is mainly classified into two types : senile type of Alzheimer's disease (STAD) and cerebral ischemia-induced one. As animal models of cerebral ischemia, a couple of types in rats have been introduced : one is the occlusion of bilateral carotid arteries-induced forebrain/global ischemia and the other is the occlusion of middle cerebral arteries-induced focal/regional ischemia. In contrast, rats with cognitive impairment caused by surgical lesion of basal forebrain (nucleus basalis Meynert) as well as entorhinal cortex have been used as models of STAD. Although the etiological mechanism of STAD has never been clarified, it is presumed that β/A4 amyloid proteins produced from amyloid precursor proteins (APP) could be involved in neuronal toxicity, followed by memory deficiency in STAD. From this hypothesis, a preparation of transgenic mice microinjecting APP genes into fertilized eggs has been tried in many laboratories. Several senescence-accelerated animals with senile symptoms at early stages are also used as cognitive deficiency models, in particular,

senescence-accelerated mouse (SAM). In this presentation, I would like to introduce our studies on neurochemical analysis of the brain functions and effects of drugs on cognitive impairment in SAM.

SAM has been established as a model of accelerated aging by Prof. T. Takeda and his coworkers of Kyoto University. Shortened life span and early manifestation of vavions signs of senescence are observed in prone strains of SAM, of which P8 strain (SAMP8) shows dysfunction of learning and memory. We examined whether or not the content of amino acid neurotransmitters, stimulus-induced release of acetylcholine (ACh) and noradrenaline, M_1 ACh and NMDA receptors and protein kinase C in cerebral cortex and hippocampus of P8 strain are different from those in R1 strain with normal aging and cognitive function. We found that : 1) the contents of glutamate (Glu) and glutamine (Gln) were higher in those in R1, indicating higher formation and/or uptake of Glu in SAMP8 brain, 2) high K^+-evoked release of Glu and aspartate and non-neurotransmitters (Gln, alanine) was increased at 10 months in P8, suggesting fragility of nerve terminals of P8 at old stages, 3) NMDA-induced release of [^{3}H]ACh and [^{3}H]NA was markedly reduced in P8, suggesting hypofunction of the cholinergic and adrenergic systems in P8, 4) the number of several neurotransmitter receptors such as M_1 ACh, 5-HT_{1A} serotonin, NMDA receptors and the amount of protein kinase C were decreased in hippocampus of P8. These results show neuronal loss and decreased synaptic activity in the brain which are relevant to cognitive impairment in SAMP8. Furthermore we obtaind an increase in [^{3}H]PK11195 binding (a selective ligand to astroglias) in SAMP8. It is possible that

neuronal degeneration causes secondarily acceleratad gliosis in P8 brain.

We then investigated usefulness of SAMP8 in screening of cognitive enhancers and examined effects of aFGF (a peptide with neurotrophic and nootropic effects) and methanol extract from Tanjin (Salviae miltiorrhizae Radix, herb with effect improving peripheral blood flow) on memory loss. aFGF was administered s.c. into SAMP8 at 7 mg/kg once a week from 3 weeks to 9 months and the memory of these mice were measured by the passive avoidance test and the Morris water maze test. In P8 the acqisition latency was not different but retained latency in aFGF group was significantly higher in P8. In addition, densities of M_1 ACh receptors and NMDA receptor/ion channels in treated group were increased in P8 compared to R1. Tanjin extract of 500 mg/kg/day was orally administered into 4 month-old mice for 3 weeks. Treated group showed significantly improved learning in the Morris water maze task, and the increased number of NMDA receptors/ion channels in cerebral cortex, although the M_1 ACh receptors number and choline acetyltransferase activity were not changed.

In summary, animal models of cognitive impairment seem to be useful for development of cognitive enhancers, if the behavional, pathophysiological and biochemical characteristics are well analyzed and well considered in the screening test. Novel and excellent animal models and novel cognitive enhancers using the models will appear in near future.