P02.50

Hippocampal neurogenesis enhancer enhances forgetting of nicotine-induced place preference memory

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Addiction memory displays some aspect of an associative memory between pleasure induced by unconditioned stimulus (US) such as drug and conditioned stimulus (CS) such as environmental context. On the other hand, our previous study showed that increasing adult hippocampal neurogenesis by neurogenesis enhancers such as exercise and treatment with memantine (MEM), an uncompetitive antagonist of the N-methyl-D-aspartate glutamate receptor, promotes forgetting of hippocampus-dependent fear memory in mice (Ishikawa et al., 2016). In this study, we tried to develop a treatment for drug addiction by facilitating forgetting of addiction memory. To do this, we examined the effects of MEM treatment on memory for nicotine addiction using the conditioned place preference (CPP) task. Mice were exposed to the conditioned chamber consisting of white and black compartments freely for 20 min per day (day 1–4; Habituation). Then mice received systemic injections of vehicle or nicotine (0.3 mg/kg) before a 20 min exposure to white or black compartment, respectively, to learn association between white compartment and nicotine treatment (day 5–9; Conditioning). Twenty-four hours after the conditioning at day 9 (day 10), mice were exposed to the conditioned chamber freely for 20 min (Test). Nicotine group exhibited significantly more time spent in white compartment compared to vehicle group, indicating that nicotine-treated mice formed a nicotine-induced place preference memory. To examine whether increasing in adult hippocampal neurogenesis promotes forgetting of this nicotine-associated memory, mice received systemic injections of MEM (50 mg/kg body weight) once a week for 4 weeks. Importantly, MEM-treated nicotine group exhibited significantly less time spent in white compartment compared to vehicle-treated nicotine group. These observations suggest that neurogenesis enhancer promotes forgetting of memory for nicotine addiction. Forgetting of memory for addiction may be useful target to develop effective treatments for addiction disorders.

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Age related increase in cav-1 expression facilitates cell-to-cell transmission of α-synuclein in neurons

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disease. Recent evidence indicates that prion-like propagation of misfolded α-synuclein (a-syn) released from neurons to neighboring neurons may play an important role in the progression of PD. Aging is the greatest risk factor in the development of PD and caveolin-1 (cav-1) participates in aging process. In the present study, we demonstrated that cav-1 expression in brain was increased with age and more increased in the brain of A53T α-syn transgenic mice, PD animal model.

To investigate whether cav-1 increases the migration of a-syn, we experimented cell to cell transmission through dual chamber system in SH-SY5Y cell lines which is human neuroblastoma cell lines. We identified that cell-to-cell transmission of a-syn is increased in cav-1 overexpressed stable cell lines compared by control cell lines. We also elucidated that cav-1 facilitated uptake of a-syn into neurons further Lewy body-like inclusion body formation. One of the phosphorylation sites of cav-1 is Y14. It has been known that Y14 of cav-1 is phosphorylated by c-src, Fyn, Yes or c-abl. To determine if phosphorylation of cav-1 is important in cell to cell transmission and Lewy body-like inclusion body formation, we made phospho-mutant form of cav-1(Y14A). We found that cell to cell transmission and aggregated a-syn increased by cav-1 was decreased in phospho-mutant cav-1 stable cell lines.

Cav-1 might play an important role in cell to-cell transmission of a-syn and phosphorylation of cav-1 is also important in cell to cell migration of a-syn. Therefore, cav-1 may be a therapeutic target for the progression of PD and cav-1 inhibitor may also be used as a remedy for PD.

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Modulation of tau isoforms by RNA reprogramming: Functional consequences and therapeutic perspectives

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Tauopathies are neurodegenerative diseases characterized by the presence of intraneuronal aggregates of the protein tau in insoluble neurofibrillary tangles (NFTs). Tau is a microtubule-associated protein predominantly expressed in neurons, which participates in microtubule polymerization and axonal transport. Alternative splicing of exon 10 (E10) in the Tau transcript produces protein isoforms with three (3R) or four (4R) microtubule binding repeats, which are expressed in equal amounts in the normal adult human brain. Several tauopathies are associated with mutations affecting exon 10 alternative splicing, leading to an imbalance between 3R and 4R isoforms. Correction of that imbalance represents a potential therapeutical approach for those tauopathies.

Here we present our achievements using a *trans*-splicing RNA reprogramming strategy to modulate the 3R:4R tau ratio, either in cultured post-mitotic human neurons differentiated *in vitro* or into the mouse brain. Lentiviral vectors were used to express molecules that modulate E10 inclusion/exclusion by RNA *trans*-splicing with the endogenous tau transcript. Tau isoforms were quantified by qPCR and western blot. Morphological analyses and live imaging axonal transport indicate that perturbations in the tau 3R:4R ratio in human neurons impaired axonal transport dynamics without altering neuronal morphology. In a mouse model of tauopathy (htau mice) local modulation of E10 inclusion in the prefrontal cortex improved cognitive deficit, restored neuronal firing patterns and reduced insoluble and hyperphosphorylated tau contents. Moreover, local shifting of 3R to 4R tau in the striatum improved motor coordination deficits in htau mice.

Together, our results evidence some of the (dys)functional consequences of tau 3R:4R imbalance and rise the potential use of RNA reprogramming to correct tau *mis*-splicing in human tauopathies.

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TMCA attenuated the morphine dependence in mice and rats

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The effect of 3, 4, 5-trimethoxy cinnamic acid (TMCA) against morphine-induced dependence in mice and rats was investigated. Mice were pretreated with TMCA and then morphine was injected intraperitoneally; whereas rats were infused with morphine intracranially. Naloxone-induced morphine withdrawal syndrome and conditioned place preference test were performed for physical and psychological dependence, respectively. Moreover, western blotting and immunohistochemistry were used to measure protein expressions. Number of naloxone-precipitated jumps and conditioned place preference score in mice were attenuated by TMCA. Likewise, TMCA attenuated morphine dependent behavioral patterns such as diarrhea, grooming, penis licking, rearing, teeth chattering, and vocalization in rats. Moreover, the expression levels of pNR1and pERK in the frontal cortex of mice and cultured cortical neurons were diminished by TMCA. Interestingly, morphine-induced elevations of FosB/ΔFosB^{+}cells were suppressed by TMCA in the nucleus accumbens sub-shell region of mice. In conclusion, TMCA could be considered as potential therapeutic agent against morphine-induced dependence.

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Effect of alpha lipoic acid on cognitive function in mouse model of chronic cerebrovascular hypoperfusion

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The importance of vascular dementia (VaD) is increasing as the aging population increases. The antioxidant α-lipoic acid (α-LA) protects against neurodegeneration in VaD, but the underlying mechanisms remain unclear. Hence, we aimed to identify the effects of α-LA on cognitive function following chronic cerebrovascular hypoperfusion in a VaD animal model. Mice were categorized into the sham, bilateral common carotid artery stenosis (BCAS), or BCAS + α-LA group. The BCAS + α-LA group was intraperitoneally injected (100 mg/kg) once daily with α-LA for 4 weeks after BCAS surgery, while the BCAS and sham groups were injected with saline. After 4 weeks, we evaluated cognitive function and exploration behavior using the Morris water maze. After the behavioral experiment, the mice were sacrificed, and brain was obtained for western blot. The BCAS group, but not the BCAS + α-LA group, showed cognitive dysfunction in the Morris water maze. Apoptosis pathways involving poly (ADP-ribose) polymerase (PARP) cleavage, phosphorylated-mammalian target of rapamycin (p-mTOR), phosphorylated-3-phosphoinositide-dependent protein kinase-1, and phosphorylated-protein kinase B (p-AKT) were enhanced in the BCAS group than the α-LA group. The BCAS + α-LA group demonstrated less PARP cleavage and p-mTOR function than did the BCAS group. In the BCAS rodent model, cognitive dysfunction and apoptosis mediated by the phosphatase and tensin homolog/AKT/mTOR pathway were observed in the hippocampus. However, acting on the mTOR pathway, α-LA improved cognitive function and led to hippocampal cell survival. Thus, α-LA may be useful for treating VaD.

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Peripheral alterations in cytokine and chemokine levels in the young adult depressive risk group

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Background: Major depressive disorder (MDD) is one of the world's major causes of disability. The incidence of MDD increases markedly during adolescence and adolescent-onset depression is often recurrent, persists into adulthood. Early diagnostic test for MDD is very important but there is no marker which has sufficient sensitivity and specificity for clinical use. There is a growing body of evidence that aberrations in immune-inflammatory pathways affect the pathophysiology of MDD and pro-inflammatory cytokines are elevated in MDD patients. Thus, we investigated the peripheral alterations of cytokines and chemokines in the young adult depressive risk group.

Method: We recruited volunteers between the ages of 18 and 39 and divided them into depressive risk group ($n = 41$) and non-depressed control group ($n = 45$) according to psychiatric assessment criteria and structured clinical interviews. Peripheral levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), IL-1β, IL-17, C-C motif ligand 2 chemokine (CCL-2), adiponectin, and cortisol were quantified by immunoassay.

Result: The psychiatric score of the depressive risk group was at a level that be diagnosed as mild depression and there was no difference in interleukins, adiponectin, and cortisol levels between depressive risk group and control group. However, in the young adult depressive risk group, the TNF-α level was significantly increased while the CCL2 level was significantly decreased. In particular, an increase in TNF-α was observed in depressive females and a decrease in CCL2 was noted in depressive males.

Conclusion: The results suggest that some markers of peripheral inflammation may be able to distinguish between depressed subjects and non-depressed controls. However, due to the low positive predictive value of diagnoses, further investigation is needed in various age groups and various clinical settings.

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