[1] Gifu Pharmaceutical University, School of Pharmaceutical Sciences, Gifu, Japan. [2] Biological Science Research, Kao Corporation, Kanagawa, Japan. [3] Health & Beauty Research Consulting, Shizuoka, Japan. [4] Department of Pathology, Keio University School of Medicine, Tokyo, Japan.

Abstract

Objective: HYBID (Hyaluronan Binding Protein Involved in HA Depolymerization, KIAA1199) is a hyaluronan (HA) binding protein, which involves in depolymerization of HA. It is reported that *HYBID* mRNA is expressed in the lung, heart, skin and brain in murine and human. However, the role of HYBID in the brain remains unclear. In this study, we have made HYBID KO mice and evaluated its function in the central nervous system.

Methods: To investigate the role of HYBID in brain, behavioral tests were performed by using HYBID KO mice. In situ hybridization was performed to investigate the localization of *HYBID* mRNA in mouse brain.

Results: *HYBID* mRNA was expressed in the brain, especially hippocampus and cerebellum in wild-type mice, but not KO. HYBID KO mice showed decreased memory ability in a novel object recognition test. The expression of *Hyal1* and *Hyal2* mRNAs was not changed in the HYBID KO mouse brain. These results suggest that HYBID plays a key role in memory function in the brain.

Conclusion: HYBID may be involved in brain function, such as memory and learning.

Policy of Full Disclosure: None.

PT681

The protective role of erythropoietin on the cognitive power deficit of the brain and histological changes in the hippocampus of diabetic mice.

Amer Al Ansari, Ebrahim Rajab, Manal Othman, Muhammad AlNaisar, Ahmmed Almubarak

Arabian Gulf University, College of Medicine and Medical Sciences, Manama, Bahrain

Abstract

Long-term diabetes is associated with accelerated ageing of the brain as evidenced by impairment of cognitive function and motor performance as well as degenerative changes in the hippocampus. A neuroprotective role for erythropoietin (EPO) has been reported in some CNS injuries like stroke and spinal cord injury. The aim of this study was to examine the effects of erythropoietin on the induced cognitive deficits in STZ-induced diabetes mellitus. Twelve male BALB/c mice aged 5–7 weeks (20-25g) were administered streptozotocin i.p. (STZ; Sigma-Aldrich) 55mg/kg/day for 5 days. Diabetic mice were randomly assigned to either control (i.e. sodium citrate buffer i.p.) (n=6), or EPO treatment (Sigma-Aldrich) 5U/g/day (dissolved in sodium citrate buffer; i.p.) (n=6), three times per week beginning six weeks after the induction of diabetes. An additional group of six mice served as normal controls. Water maze performance by measuring the latency to reach the platform was significantly higher in the Diabetic group (92.2±5s) compared to the DM+EPO (74.8±9.6s) and control group (42.5±5.4s, ANOVA $p< 0.05$) After water maze testing, the mice were decapitated and the brains removed and processed for light microscopic evaluation of dentate region of the hippocampus. In the diabetic mice, there were degenerative changes in the dentate region of the hippocampus, in the form of cell loss and shrinkage and darkening of the nuclei of other cells compared to normal mice. In contrast, there was improvement in the neurogenesis and also in the nuclear shape of the cells of the dentate region in EPO-treated diabetic mice. Conclusion: Diabetes resulted in deterioration in the cognitive power of the brain and histological degenerative changes in the dentate region of the hippocampus. These changes were ameliorated by the administration of EPO which may be useful in the treatment of diabetic neuropathy.

PT682

A novel mutation associated autism in Neuroligin1

Moe Nakanishi[1], Takashi Arai[1], Maja Bucan[2], Xiao Ji[2], Xiaoxi Liu[1], Jun Nomura[1], Eiki Takahashi[1], Toru Takumi[1]

RIKEN Brain Science Institute, Japan, [2]University of Pennsylvania, USA,

Abstract

Neuroligins (Nlgns) are postsynaptic adherent molecules consisting of five family members (Nlgn1, 2, 3, 4X and 4Y). A number of genetic studies showed that the mutations of *Nlgn2*, 3 and 4 have been associated with neuropsychiatric disorders including autism spectrum disorder (ASD). However, only few genetic and functional analyses have been reported in *Nlgn1*.

In this study, we introduced whole-exome sequencing technique to find mutations in ASD siblings and identified a novel mutation predicted as damaging by *in silico* analysis. To uncover its functional significance, we performed comprehensive analyses both *in vitro* and *in vivo*.

We introduced this NLGN1 mutation into the mouse primary hippocampal neurons. The NLGN1 mutation altered not only subcellular localization from cytoplasm to endoplasmic reticulum (ER) but also dendritic spine induction.

To address how this mutation affects behavioral phenotypes., we generated knock-in mice with *Nlgn1* mutation by direct injection of CRISPR/Cas9 RNA with guide RNA. In a series of behavioral tests, we found several autistic traits, such as impaired social communication, in addition to hippocampal dependent spatial memory deficit. Furthermore, our biochemical studies revealed that Nlgn1 protein was significantly decreased in the forebrain of mutant mice (both whole lysate and synaptosomal fraction). These results suggest that this novel *Nlgn1* mutation is involved in ASD traits in a haploinsufficient manner and reinforce the significant association between mutations in Nlgns and neuropsychiatric disorders.

PT683

Effects of acute administration of moderate and high caffeine doses on the spatial memory and motor coordination in mice.

Sayed Almosawi, Sadiq Mahdi, Hasan Baksh, Abdulrahman Qareeballa, Faisal Falamarzi, Bano Alsaleh, Malak Alrabaani, Ali Aljalban, Amer Kamal

Arabian Gulf University, College of Medicine and Medical Sciences, Manama, Bahrain

Abstract

Caffeine is the most wildly consumed psycho-stimulant substances known to man. Caffeine has important effects on alertness. While moderate caffeine use is “generally recognized as safe” but heavy caffeine consumption has been associated with serious adverse health effects. The aim of this study was to evaluate the effects of moderate (0.1 gm/L) and high (1 gm/L) doses of caffeine administered mixed with drinking water on the learning and memory and motor coordination in mice. BLC57 mice were divided into 3 groups: control group (n=8 males, no caffeine), moderate dose group (n=8 males) and high dose group (n=8, males) were tested for spatial memory by the Morris-water

maze, and motor coordination by rotarod after caffeine administration for 7 days. Water maze performance by measuring the latency to reach the platform was significantly better in the group of mice receiving moderate dose of caffeine (30.4±7.3 s) compared to the control group latency (63.6±9.4 s, ANOVA test, $p< 0.05$) and the high dose group latency (76.9±8.5 s, ANOVA test, $p< 0.05$). Statistical analysis showed also a significant difference between the control group and the high dose group. Rota rod results showed that the mice of the moderate dose group could stay more time on the rotating rod before they fall (40.5±4.3 s, ANOVA test, $p< 0.05$) than the control group (29.9±2.8 s) and the high dose group (25.2±2.6 s). We concluded that acute administration of moderate dose of caffeine to mice can enhance their spatial memory and motor coordination. However, high dose would have opposite effect and affects negatively in their performance for spatial memory and motor coordination.

PT684

Treatment with rapamycin improves deficits of social interaction in the mice exposed in utero to valproic acid

Hiroko Murakami-Kotajima, Kazutaka Ikeda, Shigeo Uchino
Tokyo Metropolitan Institute of Medical Science

Abstract

Valproic acid (VPA) is widely used as an anticonvulsant and mood-stabilizing drug. However, since the prenatal exposure of VPA shows increased incidence of autism spectrum disorder (ASD), the administration of VPA in the pregnancy period is forbidden. In contrast, rodent pups exposed *in utero* to VPA have been used as an animal model of ASD. Recently, decreased or increased mammalian target of rapamycin (mTOR) signaling pathway was shown in VPA-exposed rodents (Nicolini et al., 2015, Qin et al., 2015). The mTOR signaling pathway regulates neuronal cell proliferation, migration and maturation, including synaptogenesis, and overactivation of the mTOR signaling has been implicated in the pathogenesis of particular forms of syndromic ASDs, such as tuberous sclerosis complex (TSC), neurofibromatosis 1, and fragile X syndrome. Treatment with rapamycin, mTOR complex 1 inhibitors, in a mouse model of TSC improved abnormal behaviors, including cognition and sociability. In this study, we investigated the effect of rapamycin on social deficits of ASD model mice exposed *in utero* to VPA. We subcutaneously injected VPA at a dose of 600 mg/kg body weight (B.W.) into pregnant mice on gestational day 12.5, and the pups were injected intraperitoneally with rapamycin (10 mg/kg B.W.) or an equal volume of vehicle once daily for 2 consecutive days. Social interaction test was performed at 24 h after the last administration of rapamycin in 5–6 week-old mice (adolescence) or 10–11 week-old mice (young adult). The administration of rapamycin showed improvement in the social deficits in both adolescence and young adult mice compared with the saline injected control mice. These results suggest that rapamycin has potential to provide an effective treatment for adolescent and young adult patients with not only particular syndromic ASD but also non-syndromic ASD.

PT685

Social experience changes remyelination through interleukin-6 in mice

Manabu Makinodan[1], Daisuke Ikawa[1], Toshifumi Kishimoto[1], Takashi Komori[1], Yuki Miyamoto[2], Yosuke Nishihata[1], Kosuke Okazaki[1], Kazuhiko Yamamuro[1], Junji Yamauchi[1], Takahira Yamauchi[1]

[1]Nara Medical University, Japan, [2]National Research Institute for Child Health and Development, Japan

Abstract

Accumulating findings have shown that psychosocial stress is implicated in the pathobiology of multiple sclerosis. Most of studies regarding psychosocial stress have focused on the onset or relapse of the symptoms, aiming to examine the effects on the "demyelination". In this study, we sought to investigate whether psychosocial stress affects remyelination, not demyelination since our previous study indicated that psychosocial stress substantially changes myelination only during myelin-developing phase. In order to accomplish this, myelin in the medial prefrontal cortex (mPFC) was depleted with cuprizone and the effects of subsequent social experience on remyelination were evaluated. Interestingly, myelination in the mPFC were severely impaired in socially isolated mice after myelin depletion. We also found that social isolation for 4 weeks increased the levels of interleukin-6 (IL-6) in the mPFC. Moreover, insufficient remyelination in the mPFC of socially isolated mice after myelin-depletion was improved by the administration of IL-6 inhibitor. To validate of the effects of IL-6 on myelination, we performed a neuron-oligodendrocyte co-culture and found that IL-6 treatment markedly interfered with myelination. This study, for the first time, provided direct evidence that social experience is associated with the extent of remyelination through IL-6 expression in mice. Together, these findings suggest that psychosocial stress might disturb remyelination though IL-6 and its relevant brain functions in patients with aberrant myelination such as MS, schizophrenia and mood disorders.

PT686

Dextromethorphan-induced serotonin syndrome is via up-regulation of 5-HT1A receptors.

Hai-Quyen Tran[1], Duy-Khanh Dang[1], Thu-Hien Thi Tu[1],The-Vinh Tran[1], Eun-Joo Shin[1], Choon-Gon Jang[2], Kuniaki Saito[3], Toshitaka Nabeshima[4], Hyoung-Chun Kim[1]

[1]Neuropsychopharmacology and Toxicology Program, College of Pharmacy, Kangwon National University, Chunchon 200–701, Republic of Korea. [2]Department of Pharmacology, School of Pharmacy, Sungkyunkwan University, Suwon 16419, Korea. [3]Department of Medical Innovation, Fujita Health University Graduate School of Medical Sciences, Japan.[4]Department of Regional Pharmaceutical Care and Sciences, Graduate School of Pharmaceutical Sciences, Meijo University, Nagoya, Japan.

Abstract

Objective: Serotonin syndrome is a serious adverse reaction characterized by a cluster of dose-related adverse effects that are due to increase serotonin (5-HT) concentrations in the central nervous system. Dextromethorphan (DM) has complex neuropharmacologic effects. It has been reported that high doses of DM produce serotonin syndrome in both human and animal models. 5-HT receptor activation is thought to contribute mainly to the serotonin syndrome in mice. In the present study, we have asked whether 5-HT receptor is involved in serotonin syndrome induced by DM.

Methods: Mice were treated with WAY100635, a 5-HT1A receptor antagonist, or MDL11939, a 5-HT2A receptor antagonist, 30 min before DM administration. Scores of serotonin syndrome (i.e. reciprocal forepaw treading, lateral head-weaving, hind-limb abduction, tremor, Straub tail and flat body posture) were assessed during 30 min after DM. In addition, rectal temperature was measured 30 min after DM. Serotonin levels and 5-HT1A receptor mRNA expression were examined in the hypothalamus 2 h after DM.