PT560
A comparative study of serum Tau protein and Aβ levels on intestinal endotoxemia among Alzheimer’s disease rats and in Chinese sample of Alzheimer’s disease patients and healthy controls
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Abstract
Objective: Early our animal experiments study showed that AD rats occurs intestinal endotoxemia (IETM), and with the increasing of endotoxin, the Tau protein and Aβ increased and promote the generation of AD. Study on the change of endotoxin Tau protein and Aβ levels on intestinal endotoxemia on Alzheimer’s disease rats and in Chinese sample of Alzheimer’s disease patients and healthy controls.

Methods: The AD model of wistar rats were produced by injecting D-galactose and AlCl3, for 90 days. From January 2014 to January 2015, 40 subjects were selected from Hospitals and Nursing Homes at Taiyuan City and Perking, and control group were from communities. Neurocognitive function was detected by neuropsychological tests with the Mini mental state examination (MMSE) and Alzheimer’s disease assessment scale cognitive subscale (ADAS-cog); LPS level was detected by CE TAL; TNF-α, IL-10, TNF-β, NO were determined by ELISA; the apoptosis of brain cell were detected by TUNEL.

Results: Compared with the control group, the AD rats group had longer latency (P<0.05) and more error times (P<0.05) in Morris water maze test, and LPS, TNF-α and Tau protein and Aβ levels were increased (P<0.05). MMSE score in the patients with AD were significantly lower than the healthy elderly (P<0.01), ADAS-Cog score in patients with AD were significantly higher than the healthy elderly (P<0.01); AD patients’ and healthy controls LPS, TNF-α, Tau protein and Aβ were significantly higher than the healthy elderly (P<0.01).

Conclusion: AD rats and patients with AD and healthy controls were all accompanied intestinal endotoxemia and that may be a new risk factors in the development in the process of happen of AD, Tau protein and Aβ role is unique, and also proved a powerful evidence of Alzheimer’s disease.

PT562
Alzheimer disease therapeutics candidate, SAK3 improves the cognitive functions through inhibition of amyloid beta accumulation in APP23 mice.
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Abstract
As Alzheimer disease therapeutics candidate, we have developed SAK3 (Ethyl 2’,3’-dihydro-8-methyl-2’,4-dioxo-2-peperidinospiro[2-cyclopentene-1,3’-imidazo[1,2-a]-pyridine]-3-carboxylates) (PCT/JP2013/051388). SAK3 stimulates T-type voltage-gated Ca²⁺ channels (T-VGCC) in mouse cortical slices (Moriguchi et al., J Neurochem 2012;121:44–53). We also reported that SAK3 stimulates acetylcholine release and promotes long-term potentiation in mouse hippocampus (Neuroscience 2014 abstract 265.21). We here tested whether SAK3 reduced amyloid beta (1–42) accumulation in Alzheimer model (APP23) mice. APP23 mice aged 6 and 9 months with SAK3 (0.5mg/kg, p.o.) and measured amyloid beta (1–42) levels in both soluble and insoluble fractions from APP23 mouse cortex. The chronic administration significantly reduced the amyliod beta (1–42) levels. Consistent with the reduced amyliod beta (1–42) levels, the numbers of amyloid plaques assessed by thioflavin staining were significantly reduced by the chronic SAK3 treatment. Furthermore, the cognition assessed by novel object recognition task was improved by the chronic administration. Using LC/MS/MS system, we established high sensitivity quantification system in blood to obtain proof-of-concept of SAK3 safety in human. Taken together, the novel T-type calcium channel stimulator SAK3 restored cognition ability in APP23 mice and reduced the amyloid beta (1–42) accumulation/
aggregation. However, further extensive studies are required to elucidate the underlying mechanism.

PT563
Prenatal nicotine exposure impairs the proliferation of neuronal progenitors, leading to fewer glutamatergic neurons in the medial prefrontal cortex
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Abstract
Cigarette smoking during pregnancy is associated with various disabilities in the offspring such as attention deficit/hyperactivity disorder, learning disabilities, and persistent anxiety. We have reported that nicotine exposure in female mice during pregnancy, in particular from embryonic day 14 (E14) to postnatal day 0 (P0), induces long-lasting behavioral deficits in offspring. However, the mechanism by which prenatal nicotine exposure (PNE) affects neurodevelopment, resulting in behavioral deficits, has remained unclear. Here, we report that PNE disrupted the proliferation of neuronal progenitors, leading to a decrease in the progenitor pool in the ventricular and subventricular zones. In addition, using a cumulative 5-bromo-2'-deoxyuridine labeling assay, we evaluated the rate of cell cycle progression causing the impairment of neuronal progenitor proliferation, and uncovered anomalous cell cycle kinetics in mice with PNE. Accordingly, the density of glutamatergic neurons in the medial prefrontal cortex (medial PFC) was reduced, implying glutamatergic dysregulation. Mice with PNE exhibited behavioral impairments in attentional function and behavioral flexibility in adulthood, and the deficits were ameliorated by microinjection of D-cycloserine into the PFC. Collectively, our findings suggest that PNE affects the proliferation and maturation of progenitor cells to glutamatergic neuron during neurodevelopment in the medial PFC, which may be associated with cognitive deficits in the offspring.

PT564
Involvement of astrocyte-neuron lactate shuttle dysfunction in the cognitive impairment in diabetic mice
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Abstract
Diabetes mellitus is a risk factor for cognitive dysfunction. Several investigations have pointed that hippocampus is the key brain region in diabetic cognitive impairment. However, there are no effective curatives for diabetic cognitive impairment. Since recent reports suggested that the hippocampal astrocyte-neuron-lactate-shuttle (ANLS) is essential for the memory formation, the present study was then designed to investigate the role of ANLS in the cognitive impairment of streptozotocin-induced diabetic mice. Diabetic mice exhibit cognitive impairment in the novel object recognition test and reduced long-term potentiation (LTP) of synaptic transmission in hippocampus. These behavioral and electrophysiological changes are improved by L-lactate. We observed that inhibition of L-lactate synthesis by lactate dehydrogenase (LDH) inhibitor isosafrole caused cognitive dysfunction and reduced hippocampal LTP formation in non-diabetic, but not diabetic mice. Therefore, it is possible that diabetic cognitive dysfunction might be due to the reduced l-lactate supply in the hippocampus. We also observed that the expression of LDH5 was decreased in the hippocampus of diabetic mice as compared with non-diabetic mice. The expression of monocarboxylate transporter (MCT) that transport l-lactate, especially MCT1 and MCT4 isoform, was also decreased in the hippocampus of diabetic mice. These results indicated that the production and supply of l-lactate is attenuated in the hippocampus of diabetic mice. Since l-lactate is synthesized and released from the astrocytes, the expression of glial fibriary acidic protein (GFAP) in the hippocampus was examined. GFAP-immunoreactivity was increased in diabetic mice than non-diabetic mice, indicating that the function of hippocampal astrocytes might be changed. Inhibition of astroglial l-lactate production by pharmacological inhibition of MCT or glycogen phosphorylase caused the cognitive dysfunction in non-diabetic, but not diabetic mice. Therefore, it is possible that the cognitive impairment in diabetic mice is due to the dysfunction of the ANLS in the hippocampus.