

Methods: Nine single-nucleotide polymorphisms (SNPs) of the NET gene ([rs7194148, rs28386840, rs2242446] in promoter region, [rs1532701, rs40434, rs13333066] in intron 1, [rs187714] in intron 3, [rs5569] in exon 9, and [rs42460] in exon 14) were analyzed in total 965 Han Chinese subjects. The Chinese version Tridimensional Personality Questionnaire was introduced to assess personality traits in HD patients and examined the association between personality traits and these SNPs of NET gene.

Results: No statistically significant differences in genotype frequencies of NET polymorphisms between HD patients and controls, although, individuals with A allele of rs1532701 and T allele of rs13333066 have significant protective effect in the development of HD after multiple logistic regression analysis. Moreover, the AATA haplotype frequency in block (rs1532701-rs40434-rs13333066-rs187714) has a significant association between HD patients and controls. However, the nine polymorphisms of NET gene did not influence novelty seeking and harm avoidance scores in HD patients.

Conclusion: The AATA haplotype (rs1532701-rs40434-rs13333066-rs187714) of NET gene possibly plays a protective factor in the development of HD, but NET gene is not associated with the specific personality trait in HD patients.

Policy of full disclosure: None.

P-01.046 Chronic ketamine abuse causes dysfunctions of different brain areas relevant to neurodevelopmental psychiatric disorders: Evidence from fMRI in a primate model

H. Yu¹, Q. Li², D. Wong³, L. Shi⁴, M. YT⁴, G. Lu⁴, S. Lin⁵, L. Wang⁵, M. Chen⁶, F. Pan⁵, D. Yew⁷. ¹Shandong University, Jinan, China; ²The University of Hong Kong, Hong Kong SAR, China; ³The Chinese University of Hong Kong, Hong Kong SAR, China; ⁴The Chinese University of HK, Hong Kong, Hong Kong SAR, China; ⁵Shandong University, Jinan, China; ⁶Kun Ming Medical College, Kunming, China; ⁷The Chinese University of HK, Hong Kong SAR, China

Objective: Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, and illegal use of it as a recreational drug among adolescence and young adult is rapidly growing. Many studies have showed that prefrontal dopaminergic system is particularly vulnerable to the toxic effects on cognitive functions. This suggests that chronic ketamine abuse in young people may cause a severe disruption of different brain areas relevant to psychiatric disorders.

Methods: We established a chronic ketamine abuse model using the adolescent cynomolgus monkeys administrated with ketamine once a day (1 mg/kg, i.v.) for 6 months. Blood oxygenation level dependent (BOLD) contrast images were generated through stimulating the function of somatosensory area using functional magnetic resonance imaging (fMRI). Parallel and successive behavioral were observed.

Results: Chronic ketamine abuse in younger monkeys caused obvious deficits in the ventral tegmental area (VTA)/substantia nigra (SN), parietal cortex, and cingulate cortex. Besides, some increased activities were observed in striatum (lentiform nucleus, LN), fusiform gyrus (FG) and entorhinal cortex (Ent) on the right side of the brain in the chronic ketamine administrated monkeys. Behaviour results showed significant differences of the movement in both control and ketamine groups with general and consistent decreased trend with time periods of ketamine administration.

Conclusion: Dysfunction of a projection from Ent to LN could play a role in ketamine abuse or induce epilepsy. We also found that deficit of cortical visual area in ketamine abuse model might cause a "positive schizophrenic syndrome". Moreover, hypofunction of mesocortical dopamine pathway may induce a negative symptom in psychosis, or attention deficit disorder (ADD).

Policy of full disclosure: None.

P-02. Animal Models

P-02.001 Alzheimer's disease drug galantamine, but not donepezil, improves social isolation rearing-induced deficits in prepulse inhibition via muscarinic acetylcholine receptors

Y. Ago¹, K. Koda¹, K. Yano¹, K. Takuma¹, T. Matsuda¹. ¹Osaka University, Suita, Japan

Objective: Galantamine and donepezil are used in the treatment of Alzheimer's disease. Galantamine is a rather weak acetylcholine (ACh) esterase inhibitor, but it has additional allosteric potentiating effects at nicotinic ACh receptors (nAChRs). Clinical studies show that galantamine improves negative and cognitive symptoms in schizophrenia, while donepezil does not. In this circumstance, we have found that both galantamine and donepezil improved deficits in prepulse inhibition (PPI), sensory information-processing deficits, in apomorphine-treated mice but only galantamine improved PPI deficits in socially isolation-reared mice (Psychopharmacology, 2008). This paper investigates the mechanism of the beneficial effect of galantamine in a model of social isolation rearing-induced PPI deficits.

Methods: Three-week-old male ddY mice were housed either in groups or isolated in cages of the same size for more than 6 weeks. PPI, microdialysis and Ca²⁺ imaging experiments were done as previously reported (Br. J. Pharmacol., 2005; 2009).

Results: Galantamine-induced improvements of PPI deficits were blocked by the muscarinic ACh receptor (mAChR) antagonists scopolamine and telenzepine (preferential for M1 subtype), but not by the nAChR antagonists. Like galantamine, the mAChR agonists oxotremorine and N-desmethylozapine (selective for M1 subtype) improved isolation rearing-induced PPI deficits. Although M1-mAChR expression in the prefrontal cortex and hippocampus was not altered by isolation rearing, N-desmethylozapine-induced increases in prefrontal dopamine levels was reduced in isolation-reared mice, indicating the reduction of M1-mAChR function. With regard to the mechanisms of galantamine-induced activation of mAChRs, we found that galantamine, like donepezil, increased extracellular ACh levels in the prefrontal cortex. However, donepezil inhibited carbachol-induced Ca²⁺ signal, which was blocked by telenzepine, in SH-SY5Y cells, whereas galantamine did not. This suggests that donepezil has antagonistic activity for M1-mAChRs.

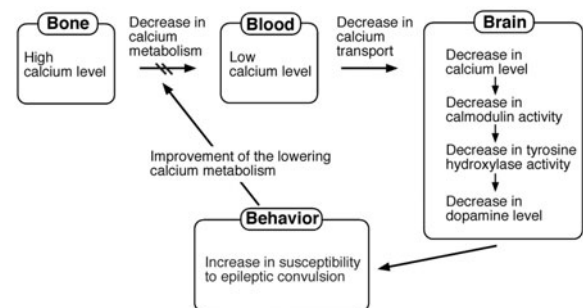
Conclusion: Galantamine improves isolation rearing-induced PPI deficits via mAChRs, and the different effects of galantamine and donepezil on M1-mAChRs may explain the difference in the clinical effects of these drugs.

Policy of full disclosure: None.

P-02.002 Disorders of dopaminergic functions in epileptic mice

K. Akiyama¹, D. Sutou¹. ¹University of Tsukuba, Japan

Objective: EL mouse is an inbred strain, derived from ddY mice, with convulsive tendencies. Violent tonic-clonic convulsions occur in adult EL mice as a result of postural stimulation. Neurochemical disorders in EL mice were investigated as a possible model for seizure mechanism.



Methods: Calcium levels were measured biochemically. Dopamine and its related substances were analyzed quantitative