PS10
Prospective Analysis of the incidence in Anxiety affected by Physical Diseases in Late Life
Sang Dae Kim
Chonnam National University Hospital, Republic of Korea

Abstract
Objectives: This study aimed to investigate the associations between physical diseases and prevalent / incident anxiety in a community dwelling older population aged 65 years or over.
Methods: 1204 people aged 65 years or over evaluated at baseline, and 909 (75.4%) were followed two years later. Anxiety was identified at both evaluation points using the questions from the community version of the Geriatric Mental State Schedule together with diagnostic algorithm, the Automated Geriatric Examination for Computer Assisted Taxonomy. Reported physical diseases covering 11 common and generally chronic health problems were ascertained. Covariates included were age, gender, education, living area, accommodation status, past occupation, current occupation and marital status.
Results: In multivariate analyses, prevalent anxiety was independently associated with 9 of 11 physical diseases (arthritis or rheumatism, eyesight problems, hearing difficulty, persistent cough, asthma, hypertension, heart disease, gastrointestinal problems, and unilateral paralysis or weakness); and incident anxiety was independently associated with 2 physical diseases (arthritis or rheumatism and heart disease). Both prevalent and incident anxiety were significantly associated with increased number of physical diseases.
Conclusion: Certain physical diseases were identified as risk and/or precipitating factors for anxiety in elders. Appropriate intervention and treatment of physical diseases might mitigate the morbidity of anxiety in late-life.
Key Words: Physical disease, Anxiety, Aged, Epidemiology, Longitudinal study

PS11
Diazepam suppresses the stress-induced excessive dopaminergic release in the amygdala of methamphetamine-sensitized rat
Takaaki Kawanoto
Tokyo Women’s Medical University, Japan

Abstract
Diazepam is widely used in the treatment of various psychiatric disorders, but during clinical practice, the proper use of other psychotropic drugs is based on symptom classification and experience. We carried out this research for the purpose of clarifying the biological basis to contribute to better medication.
We used the rats that have stress-vulnerability because of methamphetamine-sensitized, which are regarded as biological models of psychiatric disorders. We also use the skill of fear stress conditioning with them, we researched the effect of diazepam using variation of the extracellular DA in the amygdala as the indicator, which is anatomical center of the affect. We inserted a probe in an amygdaloid body by an operation maneuver and we gathered dopamine using microdialysis and analyzed it. We also did behavior experiment to see the relationship between variation of dopamine and freezing behavior.
As the results, diazepam suppressed stress-induced extracellular DA increase of amygdala. Furthermore, diazepam suppressed stress-induced extracellular DA increase of amygdala of methamphetamine-sensitized rats which is give fear stress conditioning.

We already reported in previous time that similar phenomena occur at some kinds of antipsychotic drugs and mood stabilizers. We assume that these phenomena are important as pharmacodynamics of the psychotropic drugs, and this time we report this biological basis also in diazepam for the first time.

PS12
Screening novel compounds for behavioural effects: repurposing epigenetic drugs for psychiatry
Dong Yao Wang, Jian Jin and Albert Hung Choy Wong

Abstract
Background: Mood and anxiety disorders are the leading causes of disability in established market economies such as in Canada. Current anxiolytic drugs have undesirable side effects. Thus better treatments are needed. Existing antidepressants with anxiolytic effects have been shown to reduce the level of G9a, a histone methyltransferase that methylates lysine 9 of histone H3 (H3K9). The methylation status of H3K9 plays an important role in mediating epigenetic responses to environmental stress. Thus, we reason that deliberately targeting G9a may be an effective strategy to discover new anti-anxiety medications.
Hypothesis: We hypothesize that the G9a inhibitors UNC0642 and A-366 will have anxiolytic-like effects in established animal models of anxiety.
Method: C57BL/6 mice were treated chronically (14 days) with 1mg/kg, 2mg/kg or 5mg/kg of UNC0642 or A-366. The anxiolytic-like effects of UNC0642 and A-366 on mouse behaviour were measured in the elevated zero maze (EZM), the marble burying test (MB) and on novelty suppressed feeding (NSF).
Results: Chronic treatment of A-366 increased the amount of time mice spent in the open arm of the EZM, decreased the number of marbles buried and decreased latency to eat in the NSF test. Chronic treatment of UNC0642 increased the amount of time mice spent in the open arms of the EZM but did not affect MB or NSF behaviours.
Conclusion: UNC0642 and A-366 showed dose-dependent anxiolytic-like effects on mouse behaviour with chronic treatment. The anxiolytic-like effect was likely due to G9a inhibition, given the distinct chemical structures of the two G9a inhibitors. Further experiments are needed to examine the underlying molecular and transcriptomic changes associated with behavioral changes.
Significance: These data increase knowledge of novel molecular pathways that regulate symptoms of human psychiatric disorders, and will lay the foundation for further efforts to discover new and better treatments for these important illnesses.

PS13
Role of the hypothalamic µ-opioidergic systems in the anti-tumor immune response
Yusuke Hamada (1), Yoshihiko Tasaki (2), Kana Morita (1), Wataru Ito (1), Yuri Fujimori (1), Michiko Narita (1), Hideki Tamura (3), Masami Suzuki (4), Naoko Kuzumaki (1), Kazunori Aoki (4), Akihiro Yamanaka (5), Minoru Narita (2, 5)
(1) Dept. Pharmacol., Hoshi Univ., Tokyo, Japan (2) L-Stat, Hoshi Univ., Tokyo, Japan (3) Div. Cancer Pathophysiol., NCCRI, Tokyo, Japan (4) Div. Mol. & Cell. Med., NCCRI, Tokyo, Japan (5) Dept. Neurosci.II, RIEM, Nagoya Univ., Nagoya, Japan

Abstract
The suppression of anti-tumor immune responses was considered as the prime factor in the tumor growth. Additionally, cancer inactivates the mechanism of host immune surveillance.
On the other hand, β-endorphin, a cleavage product of pro-opiomelanocortin (POMC), is an endogenous µ-opioid polypeptide primarily produced by the hypothalamus. POMC neuronal cell bodies are primarily localized in the arcuate nucleus (ARC) of the hypothalamus. The terminals of these POMC neurons are distributed throughout the CNS, including the paraventricular nucleus (PVN) of the hypothalamus, which is an important area of the brain to the stress response of the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, β-endorphin released by the activation of the hypothalamic POMC neuron is believed to change innate immune function. In this study, we investigated the role of hypothalamic µ-opioidergic systems in anti-tumor immune responses using the designer receptors exclusively activated by designer drugs (DREADD) system. To perform the activation of hypothalamic POMC neurons, we generated the transgenic mice expressing Gq-coupled human muscarinic M3 DREADD (hM3Dq) protein under the control of the POMC promoter in the hypothalamus. The hM3Dq was activated by a designer drug, clozapine N-oxide (CNO). Under these conditions, CNO-induced activation of hypothalamic POMC neurons significantly suppressed tumor growth in tumor-bearing mice. This suppression of tumor growth induced by the activation of hypothalamic POMC neurons by the administration of CNO was reversed by the pre-microinjection of naloxone into the PVN. Furthermore, CNO-induced activation of hypothalamic POMC neurons significantly decreased the plasma level of corticosterone and increased the number of NK cells in the spleen. These findings suggest that β-endorphin released by the activation of hypothalamic POMC neurons may suppress tumor growth via the PVN µ-opioid receptor-mediated suppression of the stress response of the HPA axis and the activation of cell-mediated immunity associated with NK cell activation.

### PS14

**Gender specific gene-by-environment interaction effects of SLC6A4 polymorphism and childhood maltreatment on anxiety sensitivity**

Se-Won Lim1, Murray B. Stein2

1Department of Psychiatry, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea 2Anxiety and Traumatic Stress Disorder Program, Department of Psychiatry and Family & Preventive Medicine, University of California San Diego, La Jolla, CA, USA Address of Correspondence; Dr MB Stein Anxiety and Traumatic Stress Disorder Program, Department of Psychiatry and Family & Preventive Medicine, University of California San Diego, La Jolla, CA 92039-0855, USA Tel:+1 858 534 6451; Fax: +1 858 534 6460 E-mail: mstein@ucsd.edu

**Abstract**

**Purposes:** Anxiety sensitivity (AS) is a well-established characteristic that predisposes to the development of panic attack and several anxiety disorders. It has been suggested that AS is interactively influenced by genetic and environmental factors such as childhood maltreatment. Serotonin transporter gene (SLC6A4) promoter polymorphism (5-HTTLPR) is regarded as a strong candidate genetic factor for AS. The aim of this study is to examine the effect of childhood maltreatment and SLC6A4 polymorphism, and their interaction on AS by gender.

**Methods:** Participants were 139 women and 77 men recruited from undergraduate psychology students. They were requested to genotyped for the SLC6A4 polymorphism and complete the measures for AS, Connor Davidson Resilience scale (CDRS) and childhood trauma questionnaire (CTQ). We classified the SLC6A4 polymorphism into the three functional triallelic genotypes: La/La; La/Lg or La/S; and Lg/Lg or Lg/S or S/S. The interaction and main effects of SLC6A4 polymorphism and childhood maltreatment on AS were analyzed by general linear models in all subjects and then in gender-stratified groups. All of the analyses were repeated using the classical biallelic classification without separating Lg from La.

**Results:** High AS score was observed in female gender and participants with childhood maltreatment. In GLM analysis for AS in total subjects, there were significant main effects of gender (p=0.011) and CDRS but interaction effect between SLC6A4 genotype and childhood maltreatment was not observed. However, in separate GLM models by gender, the interaction effect was significant in females (p=0.044) but not in males. In males, there was significant main effect of childhood maltreatment (p=0.039) only. When we perform same analyses using biallelic classification, these gender specific interaction effect were not observed.

**Conclusions:** Our results suggest that there is gender specificity of the effects of the SLC6A4 polymorphism, childhood maltreatment, and their interaction on AS.

### PS15

**Can gene therapy treat anxiety? – Overexpression of Neuropeptide S using adeno-associated viral vectors**

Tillmann S1, Elbrønd-Bek H1, Gotzsche CR1, Christiansen SH1, Mathé AA1, Woldbye DP2, Wegener G1

1Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Denmark 1Laboratory of Neural Plasticity, Department of Neuroscience and Pharmacology, University of Copenhagen, Denmark 2Section of Psychiatry, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

**Abstract**

**Objective:** Anxiety disorders have a lifetime prevalence of almost 30% and pose a huge burden on both patient and society. Available treatment options commonly induce adverse effects, urging the need for novel compounds. Neuropeptide S (NPS) has attracted attention due to its anxiolytic properties in rodents. The present study investigated the impact of NPS overexpression on anxiety-related behavior by infusing a recombinant adeno-associated virus (rAAV) into the medial amygdala.

**Methods:** Using stereotaxic surgery, viral vectors (rAAV-NPS vs. rAAV-Empty) were injected bilaterally into the medial amygdala of male adult Wistar rats using a thin glass micro-pipette. Behavior was characterized using standard anxiety, locomotion and depression tests (Elevated plus maze (EPM), Light/dark box (LDB), Open field (OF), Forced swim test (FST)). Immunohistochemical stainings were performed to verify overexpression of NPS. Statistical significance of differences between treatment groups was assessed using an independent samples t-test.

**Results:** Results showed that the experimental group (rAAV-NPS) spent significantly more time on the open arm in the EPM paradigm compared to the control group (rAAV-Empty), indicating an anxiolytic effect of NPS (p=0.018). Importantly, this anxiolytic effect could be delineated from locomotion, since no treatment differences across conditions were observed in the OF. Similarly, no confounding effects could be found when measuring body weight or depression-related behavior. Histology revealed NPS-positive cells in the medial amygdala in the experimental but not control group, pointing towards successful transduction.

**Conclusions:** This is the first study successfully demonstrating anxiolytic properties of NPS via transgenic overexpression. Our results are largely consistent with studies elucidating the role of NPS in acute treatments, therefore providing evidence for the