PS03
Plasticity-augmented psychotherapy for refractory depressive and anxiety disorders
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Abstract
Psychotherapy and pharmacotherapy have been the mainstays for the treatment of depression and anxiety disorders during the last century. However, treatment response has not improved in the last few decades. For instance, only half of all patients respond to mainstay antidepressants. To fulfill the needs of the remaining patients, there is a need to find treatments with better efficacy. The addition of psychotherapy to antidepressant treatment has been proven to be superior to either treatment alone. However, the time costs of psychotherapy limit its use for clinicians and patients. Advancements in neuroscience have contributed to an improved understanding of the pathogenesis of depressive and anxiety disorders. In particular, recent advances in the field of fear conditioning provide valuable insight into the treatment of refractory depressive and anxiety disorders. In this review, we studied the reconsolidation-updating paradigm and the concept of epigenetic modification, which has been shown to permanently attenuate remote fear memory. This has implications for drug-augmented psychotherapy. Future research on more sophisticated psychotherapy techniques will make this treatment modality more favorable to both clinicians and patients.

PS04
The changes of emotional behavior in a free fatty acid receptor 1, GPR40/FFAR1, deficient mice
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Abstract
A free fatty acid receptor 1 (GPR40/FFAR1) is a G protein coupled receptors which are activated by PUFA including arachidonic acid or docosahexaenoic acid. Our previous study demonstrated that activation of brain GPR40/FFAR1 exerts an antinociceptive effect mediated by the modulation of descending pain control system, and also produced antidepressant-like effect in forced swim test. Thus, we propose that PUFA-GPR40/FFAR1 signaling in the central nervous system could have a various physiological function. Recently, the decrease of polyunsaturated fatty acids (PUFA) in the brain is closely related to the episode and pathological mechanism of psychiatric diseases associate with emotional disorder such as depression and schizophrenia. However, the detail mechanisms remain unknown. In this study, we investigated whether the deficiency of GPR40/FFAR1 signaling have negative effect against emotional behavior. Emotional behavior in wild and GPR40 deficient (KO) male mice was evaluated at 5–10 weeks of age and by elevated plus maze test (EPM), open field test, social interaction test and sucrose preference test. The EPM revealed that the KO mice showed reduced anxiety-like behavior. Locomotor activity or social interaction behavior is similar between wild and KO mice. In sucrose preference test, the KO mice showed reduced sucrose preference and intake. Thus, these results suggest that brain GPR40/FFAR1 is associated with the regulation of anxiety behavior and sucrose intake in male mice.

PS05
Amelioration of PTSD-like Behavior by Melatonin in FABP3 Null Mice
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Abstract
Background and Objective: We recently reported that fatty acid binding protein 3 (FABP3, H-FABP) binds to the intracellular loop of dopamine D2L receptor and that FABP3 null mouse reveals dysfunction of dopamine-regulated motor coordination (J Neurosci 2010;30:3146: J Biol Chem 2014;289:18957). We here documented that FABP3 null mouse also exhibits an enhanced anxiety and impaired memory extinction like PTSD.

Methods: Wild type mice (C57BL6) and FABP3 null mice underwent fear conditioning once a day with consecutive 5 days and measured the fear acquisition and extinction for 35 days. When mice were administrated with melatonin receptor agonist, the drug was orally administrated once a day.

Results: The acquisition of contextual fear memory in FABP3 null was not distinguished from those in wild type mice. However, FABP3 null mice had deficits in extinction of contextual fear memory. For example, in one month after exposure to contextual stimulation, wild type mice significantly reduced the elapsed time until entering the chamber given footshock. The elapsed time remained elevated in FABP3 null mice, suggesting the deficits in the extinction. Likewise, the cFos expression in the amygdala after exposure to conditional contextual stimuli remained elevated in FABP3 null mice but declined in the wild type mice at one month later. The administration of melatonin receptor agonist completely improved PTSD-like behaviors in FABP3 null mice.

Conclusion: FABP3 null mice are novel model of PTSD, which is rescued by melatonin. These works are supported by Kakenhi 26102704 (K.F.). The authors have no financial conflicts of interest to disclose concerning the presentation.

PS06
Prefrontal dopamine-dependent plasticity mediates relapse in an animal model of anxiety disorders
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Abstract
Anxiety disorders are often treated with cognitive-behavioral interventions such as exposure therapy. Fear conditioning and extinction are used in animal models of anxiety disorders and their treatment. Prevention of relapses is a major challenge in treating anxiety disorders. About 40% of patients in remission experience a relapse. In experimental animals, fear can be reinstated by a week footshock (reminder shock) after successful extinction. However, neural circuit mechanisms responsible for fear reinstatement are poorly understood. To identify brain regions involved in processing fear reinstatement, we mapped the regional expression of the inducible immediate early gene, c-Fos. c-Fos expression was elevated in the infralimbic cortex (IL) and lowered in the medial subdivision of the central nucleus of the amygdala (CeM). Electrophysiology experiments revealed that
Neuronal encoding of anxiety in the bed nucleus of the stria terminalis
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Abstract
The bed nucleus of the stria terminalis (BNST) is important for anxiety behavior and its activity is associated with increased anxiety. However, how individual BNST neurons encode anxiogenic stimuli is unclear. Here, we employed in vivo calcium imaging and optogenetics in freely behaving mice and examined the neuronal encoding of anxiety in the BNST. First, we expressed a calcium indicator, GCaMP6s, in CaMKII-expressing BNST neurons. We implanted a microendoscope above the BNST and interfaced it with a miniaturized fluorescence microscope. These mice were exposed to the elevated plus maze (EPM), in which they spent more time in closed arms than open arms. Some BNST neurons preferentially increased their activity in open arms, and others preferentially increase their activity in closed arms, suggesting that neurons encoding anxiogenic and anxiolytic stimuli are both present within BNST. Second, we tested whether prepronociceptin (PNOC)-expressing BNST neurons respond to either anxiogenic or anxiolytic stimuli. PNOC is a precursor for Nociceptin/orphanin FQ and is highly expressed in a subset of BNST neurons. We expressed GCaMP6s in BNST PNOC neurons. PNOC neurons were activated in open arms but not in closed arms, suggesting that they only encode anxiogenic stimuli. Third, we explored the functional role of BNST PNOC neurons. We expressed channelrhodopsin-2 in BNST PNOC neurons and implanted optical fibers above the BNST. Photostimulation of PNOC neurons decreased the time spent in open arms and the open arm entries in the EPM. In addition, we targeted halorhodopsin to BNST PNOC neurons. Photoinhibition of PNOC neurons increased the time spent in open arms and the open arm entries within the EPM. These experiments demonstrate that PNOC neurons are sufficient and necessary for anxiety-like behavior. These results suggest that BNST includes both neurons encoding anxiogenic and anxiolytic stimuli and that BNST PNOC neurons encode anxiogenic stimuli and promote anxiety-like behavior.

PS08
Phenotypic analysis of a mouse model for 15q25.2–25.3 deletion syndrome
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Abstract
Human chromosome 15q25.2–25.3 deletion syndrome has recently been reported as one of the copy number variations associated with intellectual delay (ID) and mental retardation (MR) (Cooper et al., Nat. Genet., 2011). Patients with 15q25.2–25.3 (660 Kb, include 7 genes, ZSCAN2, WDR73, NMB, ZNF592, ALPK3, SLC28A1, and PDE8A) microdeletion manifest variable clinical features, including mild motor delay, myopathy, mild cognitive deficits, and ASD (autism spectrum disorders)-like symptoms. So far causal factors and mechanical evidence relevant to neuropsychiatric phenotypes have not been addressed. To analyze the consequence of 15q25.2–25.3 deletion, we developed animal model of human 15q25.2–25.3 heterozygous haploinsufficiency by chromosome engineering. Although this mutant mouse harboring 0.5 Mb deletions in chromosome 7 that corresponds to human 15q25.2–25.3 appeared normal and displayed no gross abnormalities so far, sequential behavioral analyses identified anxiety phenotypes in both open-field and elevated-plus maze tests. This mutant mouse also showed behavioral inflexibility in reversal learning test of Barnes maze although its hippocampal dependent spatial learning and memory tasks are normal. We report our progress of phenotypic analysis and discuss about its future perspectives.

PS09
Pregnant mice exposure to extreme level of oxytocin influences emotional and social behaviors of the offsprings after growing up
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Abstract
It has been reported that maternal stress during pregnancy increases the risk of psychiatric disorders of the offspring. In response to stress, the levels of various hormones, including glucocorticoids, catecholamines, neuropeptides, are increased. Oxytocin is also one of these stress-related hormones, while oxytocin is well known to play important roles in social interactions, including attachment between mother and child, as well as reproductive functions. Acute stress leads to rapid release of oxytocin from the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. In this study, we examined the effects of prenatal oxytocin exposure in mice to future emotional and social behaviors. From embryonic days 8.5 to 14.5, pregnant animals were injected with oxytocin solution once per day, whereas control animals were treated with saline. The offspring mice were tested for emotional and social behaviors at 10–15 weeks of age. Mice prenatally treated with oxytocin showed significantly increased anxiety behavior compared with control mice in the elevated plus maze test. In addition, 3-chambered social approach test indicated that mice prenatally treated with oxytocin showed significantly lower social behaviors than saline-treated mice. On the other hand, prenatal oxytocin treatment exerted no significant differences in depression-like behaviors in forced swim test. There were no significant differences in the number of oxytocin neurons in both PVN and SON between mice which took prenatal oxytocin- and saline treatments. Our results indicated that prenatal oxytocin exposure influences anxiety and social behaviors after growing up, and therefore, increased level of oxytocin evoked by maternal stress needs to be aware as a risk indicator of deteriorating mental health of the offspring.