PM310
Pregabalin prevents morphine-induced neuroadaptation in VTA DA neurons and reduces morphine self-administration and withdrawal in mice.
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Abstract
Gabapentinoid, pregabalin, is widely used to treat epilepsy, neuropathic pain, fibromyalgia and generalized anxiety disorder. Pregabalin is believed to lack abuse potential, but it is also known to produce an euphoric state in some patients. Dopamine (DA) neurons in the ventral tegmental area (VTA) play a key role in the mechanisms of action of addictive drugs. Particularly, addictive drugs including morphine induce glutamatergic neuroplasticity in VTA DA cells. The goal of this study was to determine whether (1) pregabalin alone can induce persistent neuroadaptations in VTA DA neurons like other addictive drugs and (2) whether it alters reinforcing properties of morphine.

We used whole-cell voltage-clamp recordings to study synaptic responses of VTA DA neurons in slices. Neuroplasticity was assessed as AMPAR/NMDAR-mediated current ratio. Using C57BL/6J mice we examined withdrawal symptoms, locomotor activity and intravenous self-administration.

We first demonstrated that non-sedative doses of pregabalin (50–200 mg/kg, i.p.) did not alter the AMPAR/NMDAR ratio in VTA DA neurons at 24 h after the treatment. Mice did not self-administer it more than saline. Next, we showed that pretreatment with pregabalin (50 mg/kg, i.p.) persistently suppressed morphine (10 mg/kg, s.c.) treatment-induced neuroplasticity in the VTA DA neurons. Importantly, the same dose of pregabalin attenuated morphine-induced hyperlocomotion and self-administration of morphine. Furthermore, it also suppressed withdrawal symptoms, such as jumps and tremor episodes in morphine-treated mice.

Our results are consistent with nonaddictive profile of pregabalin, although recently its abuse has been increasing in drug addicts. Gabapentinoids may have potential for development of novel treatment strategies for opioid addiction.

PM311
Possible role of CDH13 in nicotine dependence: Investigations on mouse neural progenitors and schizophrenia patients
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Abstract
Nicotine dependence is one of the most significant public health problems worldwide, and much more common in schizophrenia patients (smoking rates in schizophrenia range from 45 to 88%, compared to < 20% in the general population). While many studies have revealed nicotinic acetylcholine receptor (nAChR) subunits are associated with nicotine dependence both genetically and functionally, genome-wide association studies and candidate gene analysis for nicotine dependence have identified Cadherin13 (CDH13) as one of susceptibility genes other than nAChR genes. In addition, we previously reported that genetic variants of CDH13 promoter are associated with schizophrenia for the first time. However, no previous work has investigated the function of CDH13 in nicotine dependence or the genetic association of CDH13 with high smoking rates in schizophrenia.

In this study, we attempted to evaluate the function of CDH13 in nicotine dependence and whether a genetic variant of CDH13 contributes to smoking status in schizophrenia patients.

Our study suggests that CDH13 reduction may contribute to nicotine dependence via upregulation of CHRNA3 and CDH13 may be associated with genetic susceptibility to nicotine dependence in schizophrenia.

This study was carried out in strict accordance with the Guidelines for Animal experiments and the Ethical Committee for Genetic Studies of Kobe University Graduate School of Medicine.

PM312
Combination of levo-tetrahydropalmatine and low dose naltrexone: a promising treatment for the prevention of cocaine relapse
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Abstract
Relapse to drug use is often cited as the major obstacle in overcoming a drug addiction. While relapse can occur for a myriad of reasons it is well established the complex neuroadaptations, which occur over the course of addiction, are major factors. Cocaine use specifically, induces alterations in the dopaminergic as well as other monoaminergic neurotransmissions that can lead to cocaine abuse and dependence. Evidence also suggests that adaptations in the endogenous opioids play important roles in pathophysiology of cocaine addiction. Following this premise, we investigated a combination medication, levo-tetrahydropalmatine (l-THP) and low dose naltrexone (LDN), targeting primarily dopaminergic and endogenous opioid systems as a cocaine relapse prevention treatment. In the present study Wistar rats were used to assess the effects of l-THP and LDN on cocaine self-administration, drug-seeking behavior during cocaine reinstatement, spontaneous locomotion and effects on the endogenous opioid system. The combination of l-THP and LDN reduces drug-seeking behavior during reinstatement more efficaciously than l-THP alone. Additionally, the combination of l-THP and LDN attenuates the sedative locomotor effect induced by l-THP. Furthermore, we revealed that treatment with the combination of l-THP and LDN has an upregulatory effect on both plasma β-endorphin and hypothalamic POMC that was not observed in l-THP-treated groups. These results suggest that the combination of l-THP and LDN has great potential as an effective and well-tolerated medication for cocaine relapse prevention.