neurons with red stoplasma were denser in sectors than the other neurons. Glutamate immunopositivity has detected in hippocampal neurons, neuropil, habenular nuclei and cortical tractus. Number of neurons were significantly less in morphine group compared to controls and there were no significant difference between control and agmatine treated groups.

**Conclusion:** According to the findings of the current study repeated morphine withdrawal syndrome can cause damage on learning-memory and glutamatergic system may play a role at least a part. Agmatine has a clear protective role on memory functions. Further research is necessary to understand the mechanism underlying.

**PM285**  
Neuropharmacological effect of ketamine-induced hyperlocomotion modulated by age in the C57BL/6J mice  
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**Abstract**  
**Background:** Ketamine, an antagonist on N-methyl-D-aspartate (NMDA) receptor, can produce neurobehavioral changes ranging from mood alterations and psychotic episodes in human to hyperactivity and stereotyped motion in mice. In the study, we tested the pharmacological properties of ketamine on anxiety, locomotion and motor activity.

**Materials and Methods:** Subjects were C57BL/6J mice with age of 6 and 12 weeks at the time of testing. Mice were housed in a temperature- and humidity-controlled vivarium under a 12h life-dark cycle with ad libitum access to food and water. Sensitivity to acute intoxicating effect was assessed using accelerating rotarod under given doses of ketamine (0, 10, 25, 50mg/kg, respectively). The elevated plus-maze (EPM) was used to evaluate the anxiety-like behaviors. Open field with videotracking system was adapted to measure the motor responses following acute and chronic ketamine injections.

**Results:** The results demonstrated that the ketamine could dose-dependently potentiate the motor ataxia and significantly increased the open-arm entries at the dose of 25mg/kg through EPM assessment. Ketamine produced hyperactivity at the age of both 6 and 12 weeks. The adolescent mice significantly increased the total moving distance and speed compared to the adult group.

**Conclusion:** These findings suggest that the effect ketamine is regulated by age and potentiating the sensitivity in the adolescent mice.

**PM286**  
Cocaine modifies preference of choice in rat gambling task  
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**Abstract**  
**Background and aims:** Rat gambling task (rGT) is one of the most sophisticated animal model which shares many of the features of the human gambling tasks including uncertainty, reward and punishment. In this model, how cocaine affects the preference of choice has been examined.

**Methods:** Rats were trained in a touch screen chamber to learn the relationships between 4 different light signals on the screen and accompanied reward outcomes and punishments set up with different schedules, for one session of 30min each day. Then, they were allowed for free choices out of 4 different light signals. Once animals showed a stabilized pattern of preference, they were given 7 days of either saline or cocaine IP injections (a single injection per day) followed by 2 weeks of withdrawal. Then, their preference of choice was re-tested in rGT chambers.

**Results:** Depending upon their preference of choice, rats were separated as either risk-averse or risk-seeking groups. However, when they were exposed to cocaine, rats in the risk-averse group significantly changed their preference toward more disadvantageous choices.

**Conclusions:** These results indicate that cocaine influences even different types of decision-making behavior as in gambling task, which is not directly relevant with obtaining cocaine itself, implying that they may aggravate pathological symptoms of bad choices, resulting in negative consequences, observed in the patients with behavioral addictions.

**Keywords:** pathological gambling, cocaine, decision making, behavioral addiction

**PM287**  
Mixtures of opioid receptor agonists and cannabinoi

**Abstract**  
Mu opioid receptor agonists remain the drugs of choice for treating moderate-severe pain despite their well-documented adverse effects (constipation, respiratory depression, abuse). Kappa opioid receptor agonists also have antinociceptive effects although adverse effects (dysphoria, hallucinations) have precluded their use in the clinic. One strategy for reducing or avoiding the adverse effects of opioid receptor agonists (mu and possibly kappa) is to combine them with drugs that exert antinociceptive effects through nonopioid mechanisms. The need for much smaller doses of each drug in a drug mixture, to achieve the desired therapeutic effect, has the potential to avoid the adverse effects that occur with larger doses of either drug administered alone, thereby increasing the therapeutic window of both drugs. These studies used adult male rats to examine the antinociceptive effects of mu and kappa opioid receptor agonists, each administered alone and in combination with a cannabinoid receptor agonist. When administered alone (intraperitoneally), morphine (mu receptor agonist; 1.78–17.8μg/kg), spiradoline (kappa receptor agonist; 1–32μg/kg), Δ9-tetrahydrocannabinol (THC; cannabinoid receptor agonist; 3.2–32μg/kg), and CP55940 (cannabinoid receptor agonist; 0.032–1μg/kg) increased tail withdrawal latency from 50°C water in a dose-related manner. Mixtures of an opioid and a cannabinoid, in ratios of 3:1, 1:1, and 1:3, also increased tail withdrawal latency in a dose-related manner. The interaction for both mu (morphine) and kappa (spiradoline) receptor agonists with a cannabinoid receptor agonist was at least additive for all mixtures and greater than additive (synergistic) for some ratios of some mixtures. Together these results support the view that mixtures of opioids and nonopioids could provide significant therapeutic effects (for treating pain) in the absence of some ratios of some mixtures.
of adverse effects that currently limit the use of opioids in the clinic. Supported by USPHS Grant K05DA017918

PM288
Preclinical Evaluation of Neutral Cannabinoid CB1 Receptor Antagonists and Cannabinoid CB1 Receptor Negative Allosteric Modulators for Treating Drug Addiction
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Abstract

Objective: Preclinical animal studies show that cannabinoid CB1 receptor (CB1R) orthosteric antagonists/inverse agonists have strong anti-addiction effects against many addictive drugs. However, development of CB1R orthosteric antagonists/inverse agonists was terminated in 2008 due to significant side-effects (anxiety, depression, suicidal ideation) in clinical trials and use in Europe of the lead CB1R orthosteric antagonist/inverse agonist SR141716 (rimonabant). We propose that neutral CB1R antagonists (lacking inverse agonism) or CB1R negative allosteric modulators (binding to transmembrane allosteric sites rather than extracellular orthosteric sites) may have therapeutic anti-addiction potential without unwanted effects.

Methods: We evaluated the effects of these three types of CB1R ligand in animal models relating to drug addiction – including intravenous drug self-administration and drug-enhanced electrical brain-stimulation reward (BSR).

Results: We found that 1) the inverse CB1R agonist SR141716 (3, 10 mg/kg, i.p.) significantly inhibited cocaine, heroin, or nicotine self-administration and cocaine-enhanced BSR in laboratory rats; but SR141716 itself produced dysphoric effects in the BSR model; 2) the CB1R neutral antagonists AM4113 and PIMSR1 (3, 10 mg/kg) significantly attenuated cocaine, nicotine, or heroin self-administration and cocaine-enhanced brain-stimulation reward, by themselves, the two compounds had no effect on basal BSR functions; 3) the CB1R negative allosteric modulators (NAMs) GAT358 and GAT369 (10, 20 mg/kg) altered neither nicotine-enhanced BSR nor basal BSR functions.

Conclusions: Neutral CB1R antagonists appear more promising than CB1R orthosteric antagonists/inverse agonists or CB1R NAMs in medication development for treatment of drug abuse and addiction.

PM289
Reduction of sensitivity to nicotine aversion in repeated nicotine-injected rats
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Abstract

Nicotine not only stimulates brain reward circuits to establish and maintain the tobacco smoking habit, but also produces aversive reactions to nicotine after initial exposure, due to its noxious properties. To determine the effects of repeatedly exposed nicotine on the sensitivity to nicotine aversive behavior in rats, we performed the two-bottle free choice test for nicotine-injected rats in a nicotine concentration difference. At first test day, saline-injected rats showed nicotine indifference, but nicotine-injected rats more preferred nicot ine water. Whereas saline-injected rats presented increased nicotine preference during two days against a preferable low dose of nicotine, nicotine-injected rats showed no significant alteration of nicotine preference. This result implies that the repeated nicotine pre-exposure mitigates the nicotine aversive behaviors against the new nicotine choice. In a high concentration of nicotine preference test, both saline- and nicotine-injected rats showed nicotine aversive behavior but the nicotine consumption in nicotine-injected rats more increased than that of saline-injected rats. Importantly, whereas nicotine preference in saline-injected rats reduced when the dose of nicotine water increased, there was no significant difference in nicotine-injected rats. There was similar to sweet saccharine preference for positive reward and bitter quinine preference for negative avoided reward in both saline- and nicotine-injected rats, suggesting that the alteration of nicotine preference is nicotine specific, possibly via nicotine specific regulating system. Taken together, we demonstrate that repeated nicotine exposure reduce the sensitivity to nicotine aversive behaviors in rats. This phenomenon would provide a new insight to the feasibility of developing novel therapeutic agents for nicotine addiction that act by enhancing nicotine avoidance. (supported by NRF-2013R1A1A1057712 and NRF-2014R1A2A2A04007391)

PM290
Involvement of dorsohippocampal orexin-2 receptors in drug-dependency: A psychopharmacological study
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Abstract

It has been revealed that orexinergic system is engaged in reward processing and drug addiction. In this study, the effect of intrahippocampal CA1 administration of orexin-2 receptor (OX2r) antagonist on the acquisition, expression and extinction of morphine-induced place preference in male Wistar rats was scrutinized in order to investigate the effects of antagonist on suppression of drug-seeking behavior. Animals weighing 230–280 g were bilaterally implanted with two separate cannulae into the CA1 region of the hippocampus. Conditioned place preference (CPP) was induced by subcutaneous injection of morphine (5 mg/kg) during a 3-day conditioning phase. In this investigation, three experimental plots were designed; TCS OX2 29, as a selective antagonist of orexin-2 receptors (OX2rs), was dissolved in DMSO 12%, prepared in solutions with different concentrations (1, 3, 10 and 30 nM) and were microinjected into the CA1 region of the hippocampus (0.5 µl per side). Conditioning scores and locomotor activities were recorded during the test. The results demonstrate that morphine-induced CPP was remarkably attenuated in subjects which received intrahippocampal OX2r antagonist during the acquisition and expression phases. The effect of TCS OX2 29 on the reduction of morphine CPP in the acquisition phase was dose-dependent and also was more pronounced during the acquisition than the expression. Furthermore, higher concentrations of TCS OX2 29 facilitated extinction of morphine CPP and reduced the extinction period. Nevertheless, the administration of TCS OX2 29 solutions did not have any influence on locomotor activity of all phases. Taken together, these findings suggest that OX2rs in the CA1 area of the hippocampus are involved in the development