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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.

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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 nicotine 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-2013R1A1A0577112 and NRF-2014R1A2A2A04007391)
of the acquisition and expression of morphine CPP. Moreover, antagonism of OX2Rs could facilitate extinction and may extinguish the ability of drug-related cues, implying that the antagonist might be considered as a propitious therapeutic agent to suppress drug-related behavior.

References
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Synthetic cannabinoid JWH-210 induces motor impairments through the regulation of neurotransmission in tetanus toxin-treated mice
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Abstract
The problem of new psychoactive substances is emerging globally. Cannabinoid receptors mediate the action of synthetic cannabinoids, which are one of most abused drugs. Recently, cannabinoid receptors 1 (CB1R) have been reported to silence glutamatergic nerve terminals in cerebellar granule cells via synaptic vesicle redistribution. This study aimed to determine whether synthetic cannabinoid administration (0.1 mg/kg, 5 days) influences the development of biotoxin-induced deficit in neuronal homeostasis. We observed that JWH-210, a synthetic cannabinoid, induced motor impairment and decrement of vesicle-associated membrane proteins 2 (VAMP2) levels in the cerebellum of mice treated with tetanus toxin. Cerebellar glutamatergic neuronal homeostasis was hampered by JWH-210 administration, as evidenced by increased glutamate concentration levels in the cerebellum of the tetanus-treated mice. However, JWH-250, which has a lower CB1R binding affinity than does JWH-210 (K value: 1.1 × 10^{-7} M, and 2.6 × 10^{-8} M, respectively) did not exacerbate motor impairment and VMAP2 decrements in the cerebellum of tetanus-treated mice. In addition, tyrosine hydroxylase, the dopamine synthetic enzyme was downregulated in the striatum of JWH-210/Tetanus mice. These results suggest that JWH-210 may have an additive effect on the tetanus toxin-induced glutamatergic and dopaminergic neuronal dysfunction.

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Possible involvement of cannabinoid CB1 receptors in behavioral impairments after withdrawal from chronic methamphetamine administration in mice.
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Abstract
Objective: Endocannabinoid systems play important roles in physiological functions in the central nervous system, such as pain perception, appetite, psychomotor behavior, emotion, reward system and cognitive function. We previously reported that the involvement of cannabinoid CB1 receptors in the reinstatement of methamphetamine-seeking behaviors in rats. On the other hand, chronic administration of methamphetamine causes behavioral sensitization in rodents and human. However, the effects of withdrawal from chronic administration of methamphetamine on the cognitive deficits have been still unclear. In this study, we investigated relationship between cognitive deficits and development of behavioral sensitization by using the cannabinoid CB1 receptor knockout mice.

Method: Mice were subcutaneously administered methamphetamine at the dose of 1.8 mg/kg or saline, every other day for 30 or 60 days (15 or 30 injections). Behavioral sensitization was evaluated by locomotor activity in the open-field test. 10 or 30 days after withdrawal, the mice were tested a cognitive functions by object recognition test and sensorimotor gating function by prepulse inhibition test.

Result: In wild-type mice, locomotor activity was enhanced by the chronic administration of methamphetamine. Approach time to the novel object was decreased during withdrawal of chronic methamphetamine. In addition, prepulse inhibition of the acoustic startle response was suppressed during withdrawal of chronic methamphetamine. On the other hand, in CB1 receptor knockout mice, the locomotor activity was not enhanced by chronic administration of methamphetamine. Furthermore, CB1 receptor knockout mice were not impaired the cognitive function and prepulse inhibition by chronic administration of methamphetamine.

Conclusion: Our data suggest that activation of the cannabinoid CB1 receptors could lead to the development of behavioral sensitization and cognitive/sensorimotor gating deficits after withdrawal from chronic methamphetamine administration.

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Efficacy and Safety of Aripiprazole for Maintenance Treatment of Methamphetamine Dependence Following Methamphetamine Psychosis: A Naturalistic Retrospective Study
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Abstract
Objective: The objective was to determine the efficacy and safety of aripiprazole in the maintenance treatment of methamphetamine dependence following methamphetamine psychosis in Thai patients.

Methods: This was a retrospective chart review study in patients aged between 18–65 years with metamphetamine dependence who had been received aripiprazole (dose 2.5–15 mg/day) for at least 2 weeks after resolved from psychosis. Primary outcome was abstinence rate at 12 weeks which was assessed by urine toxicology. Adverse events were reported as secondary outcome.

Results: Forty-three patients were enrolled in this study. Most of them (58.1%) received aripiprazole 10–15 mg/day. The abstinence rate at week 2, 4, 6, 8, 10 and 12 were 90.70%, 88.10%, 78.13%, 76.47%, 91.67% and 75%, respectively. Parkinsonism was the most commonly found adverse events (11.63%), following by insomnia (6.98%), sedation (6.98%) and akathisia (4.65%).