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Neurocognitive Examination of Inhibitory Control and Error Processing Mechanisms In Prescription Opioid Dependence

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Abstract

Introduction: Prescription opioid (PO) abuse is a growing public health concern worldwide as evidenced by an increasing number of opioid-related hospital admissions with a striking lack of research examining the neural basis underlying cognitive symptomology. Drugs of abuse, through their impact on the dopaminergic system, are thought to disrupt the pre-frontal cognitive network regulating impulse control through performance monitoring and inhibition of goal-oriented behaviour. The objective of the present study is to examine neurocognitive processes in PO abusers (vs. healthy controls) by relying on the enhanced temporal resolution (1ms) of event-related potentials (ERPs) to track information processing abnormalities associated with cognitive control. Methods: In a naturalistic clinical study, 20 patients actively using prescription opioids and 20 healthy controls (matched for age, gender, educational level and smoking status) were assessed using a Go/NoGo paradigm, where the response to NoGo trials was evaluated. Results: Preliminary analysis reveals significantly ($p<0.05$) larger N200 and P300 amplitudes in patients (vs. controls) after successful NoGo trials. The N200 is a frontally distributed negative waveform reflecting the commencement of active inhibition, whereas the P300 is a fronto-centrally distributed positive waveform reflecting the termination of a previous inhibitory process. Following unsuccessful NoGo trials, error positivity (Pe) amplitudes were also significantly ($p<0.05$) increased in patients (vs. controls). The Pe is a fronto-central positive deflection component of the ERP representing the awareness of conscious error processing. Conclusions: These ERP results of altered cognitive control and error processing suggest the neural mechanisms underlying these cognitions are affected by chronic opioid abuse. Investigating the cognitive abnormalities experienced by PO abusers is an important factor in understanding the neural correlates of substance abuse and in predicting successful outcomes to ensure the best chance at long-term recovery for addicted individuals. Research funded by a Canadian Institute of Health Research (CIHR) grant.

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Knockdown *Piccolo* suppressed Methamphetamine-induced behavioral changes and dopamine release in the nucleus accumbens of mice

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Abstract

The *Piccolo* gene was identified as one increased molecular in nucleus accumbens (NAc) of mice which treated with methamphetamine (METH) continuously. *Piccolo* is originally reported as a Ca^{2+} sensor for regulating release of insulin in pancreas β cell. *Piccolo* is a protein of the pre-synapse, and it is comprised of domains such as PDZ, C2A or C2B mainly. The PDZ domain interacts with other pre-synapse proteins comprised of active zone. The C2A domain is including Ca^{2+} binding site, and it is considered that spatial structure changes in Ca^{2+}-binding presence. It is reported that *Piccolo* plays an important role in the neuronal synapse. However, function of *Piccolo* gene in NAc remains unclear in the drug dependence. Therefore, we investigated the physiological function of *Piccolo* in the NAc of mice, which were received METH treatment.

To clarify of *Piccolo* in the NAc, we characterized the NAc-specific knockdown mice (mi *Piccolo* mice) by adeno-associated virus (AAV) vector including *Piccolo* miRNA. METH-induced locomotor activity of mi *Piccolo* mice was reduced compared with that of AAV-mock mice (Mock mice). The mi *Piccolo* mice suppressed the METH-induced CPP formation. In the microdialysis test, the mi *Piccolo* mice exhibited lower dopamine basal levels and tendency to decrease METH-potentiated dopamine release. These results suggested that *Piccolo* in the NAc regulates dopaminergic neuronal systems and METH-dependence related-behaviors.

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Pseudoginsenoside-F11 inhibits methamphetamine dependence by regulating GABAergic and opioidergic neuronal system in the nucleus accumbens of mice

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Abstract

Objectives: Methamphetamine (METH) dependence is a global health and social problem, which is usually associated with serious psychiatric symptoms, and no effective therapeutic approaches have been identified. Pseudoginsenoside-F11 (PF_{11}) is an ocotillol-type saponin that is isolated from *Panax quinquefolius* (American ginseng). It was shown to attenuate the pharmacological effects of morphine and METH-induced neurotoxicity in mice. However, the functional roles of PF_{11} in METH dependence are still unknown. In this experiment, we investigated whether PF_{11} would affect METH-induced abnormal behaviors and then elucidated the mechanism of its pharmacological effects on METH responses.

Results: In the conditioned place preference (CPP) test, co-administration of PF_{11} and METH during the conditioning phase inhibited the development of METH-induced CPP. In addition, after developing METH-induced CPP, repeated administration of PF_{11} for 5 days decreased the CPP compared with vehicle-treated METH withdrawal group. In the locomotor activity test, co-administration of PF_{11} and METH for 6 days attenuated METH-induced locomotor sensitization compared with administration of METH alone. Moreover, *In vivo* microdialysis analyses indicated that co-administration of PF_{11} and METH for 7 days prevented METH-induced extracellular dopamine (DA) increase in the nucleus accumbens (NAc). Repeated PF_{11} administration for 7 days increased extracellular GABA levels in the NAc, whereas single administration of PF_{11} did not. Furthermore, hyperlocomotion and accumbal extracellular DA