1. **No.**

   FP01812216

2. **Title**

   Therapeutic and addictive mechanism of nicotine based on a novel animal model of Attention-Deficit/Hyperactivity Disorder

3. **Period**

   2016-2018

4. **Summary**

   The cigarette smoker rate of Attention-Deficit/Hyperactivity Disorder (AD/HD) patients is higher than the rate of general population. The smoking incentive in AD/HD patients is considered as the self-medication. The EP1 (prostaglandin E2 receptor) knockout mice showed normal circadian rhythm and AD/HD-like behavior such as impulsiveness in cliff avoidance test, decrease in sociality in social interaction test, and an impairment of object recognition memory in novel object recognition test. EP1 knock out mice showed the behavioral changes with good face validity for animal model for AD/HD. Administration of methylphenidate and atomoxetine reversed these AD/HD -like behaviors in EP1 knockout mice. Pharmacological responses to anti-AD/HD medications during behavioral tasks suggest that EP1 knockout mice have the potential to be a model with predictive validity for assessments of new therapeutics for AD/HD. Although the increase of extracellular dopamine by stimulation with high potassium was normal, dopamine D1 receptor agonist-induced phosphorylation of intracellular signaling (ERK and DARPP32) is diminished in the prefrontal cortex of EP1 knockout mice. EP1 knockout mice have the potential to be a model with constructive validity for AD/HD by hypodopaminergic function in the prefrontal cortex. The acute treatment of nicotine and galantamine ameliorated AD/HD-like behaviors of EP1 knockout mice. These improving effects of nicotine were blocked by the co-treatment with methyllycaconitine, an α7 nicotinic receptor antagonist, and/or dihydro-β-erythroidine, an α4β2 nicotinic receptor antagonist. The nicotine at the dose of ameliorating AD/HD-like behavior did not induce place preference. In conclusion, nicotine and galantamine have a therapeutic potential for AD/HD without rewarding effect.