1. No.
   2019G029

2. Title
   Study on the regulatory mechanisms of nicotine for the activity and the protein amount of tyrosine hydroxylase

3. Period
   2019-2021

4. Summary
   Midbrain dopaminergic neurons are deeply involved in reward and addiction, and it is important to investigate the dopaminergic neural transmission for understanding the molecular mechanism of drug-addiction. Tyrosine hydroxylase (TH) is the rate-limiting enzyme for the biosynthesis of dopamine (DA). We studied the effects of the oxidative stress on the activity of TH. It has been reported that DA is prone to be oxidized and forms DA oxides, such as dopamine quinone and aminochrome. We found that TH was inactivated by the incubation with N-ethylmaleimide (NEM) or DA oxides, and that Cys176 of human TH was the site of the modification by these compounds using TH mutants substituted Cys with Ala.
   We generated TH-over expressing mice using adeno-associated virus. TH-S40E mutant is stably active, while the activity of TH-wt is suppressed by DA as a feed-back inhibitory mechanism. Although the DA levels in the striatum of TH-S40E mice were not different from that of TH-wt mice, the levels of homovanillic acid, a major metabolite of DA were higher in the TH-S40E mice. We found that the TH-S40E mice were more susceptible to methamphetamine (METH), a drug of abuse, than TH-wt mice, which showed higher responses to METH than AcGFP mice as a control. Our results suggested that TH activity should be one of the determinants of susceptibility to METH and other addictive drugs.