1. **No.**

   FP01812206

2. **Title**

   Novel midbrain dopaminergic regulation by V-1/CP complex-targeted nicotinic acetylcholine receptor-dependent mechanism

3. **Period**

   2017-2019

4. **Summary**

   We have previously shown that the V-1/CP complex is essential for gene expression of dopamine biosynthetic enzymes. However, how the complex is activated and expresses physiological functions was not clear. In this research project, activation of nicotinic acetylcholine receptor promotes V-1/CP complex formation, and enhances the gene expressions of dopamine biosynthesis enzymes and dopamine biosynthesis in a complex-dependent manner. Besides, nicotine ingestion activates the V-1/CP complex to increase TH gene expression and dopamine levels, while receiving inhibitory input from GABAergic nerves via GABA receptors, which reveals the molecular mechanism of nicotine-dependent regulation of the complex formation and TH transcriptional activity. It was also shown that compounds targeting the V-1/CP complex actually promoted the formation of the complex at the mouse level and enhanced TH expression and dopamine levels. On the other hand, we also revealed mutations in V-1 and CP gene for which nicotine receptor-targeted therapy is effective or ineffective. These findings suggest that the V-1/CP complex may be involved in the therapeutic ability and vulnerability of dopaminergic disorders.