1. **No.**

   FP01809114

2. **Title**

   Elucidation of the serotonergic circuits involving in nicotine withdrawal by using optogenetics

3. **Period**

   2017-2019

4. **Summary**

Our goals were to identify the exact serotonergic raphe nuclei regulating nicotine withdrawal symptoms by using recently-developed optogenetic tools. We used transgenic mice expressing archaerhodopsinTP009 or channelrhodopsin-2[C128S] exclusively in the central serotonergic neurons to manipulate serotonergic neurons in each raphe nucleus selectively. Nicotine withdrawal symptoms were precipitated by acute injection of mecamylamine, a nonspecific nicotinic acetylcholine receptors (nAChR) antagonist, following chronic nicotine consumption. Somatic signs, anxiety-like behavior in the elevated plus-maze test, and depressive-like behavior in forced swim test were used as measures of nicotine withdrawal symptoms. Acute mecamylamine administration significantly increased ptosis occurrence in nicotine-drinking mice compared with that in control-drinking mice. Optogenetic inhibition of the serotonergic neurons in the median raphe nucleus (MRN), but not of those in the dorsal raphe nucleus (DRN), mimicked the symptoms observed during mecamylamineprecipitated nicotine withdrawal even in nicotine-naïve mice following the administration of acute mecamylamine injection. Optogenetic activation of the serotonergic neurons in the MRN nearly abolished the occurrence of ptosis in nicotine-drinking mice. The serotonergic neurons in the MRN, but not those in the DRN, are necessary for the occurrence of somatic signs, a nicotine withdrawal symptom, and the activation of these neurons may act as a potential therapeutic strategy for preventing the somatic manifestations of nicotine withdrawal.