1. No.

   2021Y013

2. Title

   The elucidation of the underlying developmental neurotoxic mechanism of nicotine using human basal forebrain cholinergic neurons

3. Period

   2021-2023

4. Summary

   It is known that smoking by pregnant women significantly impairs cognitive function in their unborn offspring. Since mouse basal forebrain cholinergic neurons (BFCN) play an important role in cognitive function, I hypothesized that nicotine would impair the differentiation of human BFCN in late pregnancy or immediately after birth, leading to subsequent cognitive dysfunction. However, existing methods to induce human pluripotent stem cells into human BFCNs are contaminated with many inhibitory neurons, and selective BFCNs cannot be obtained. Therefore, I have combined forced expression of a group of human BFCN differentiation-related transcription factors I identified with small molecular compounds for neural induction, I found that the mRNA expression of CHAT, a marker of BFCN, was markedly increased, while the mRNA expression of GAD1, a marker of inhibitory neurons, was markedly decreased. These results suggest that I have successfully developed a method for selective induction of human BFCNs to assess nicotine toxicity. Next, I improved the culture method for forebrain organoids, which I believe promotes more differentiation and maturation, and succeeded in generating forebrain organoids even from human iPS cells used in this study.