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2. Title
   A Novel Therapeutic Strategy for Ischemic Stroke based on Understanding the Nicotinic Acetylcholine Receptor Signaling

3. Period
   2022-2024

4. Summary

   Cerebrovascular disease is the most common cause of disability in the world and the second most common cause of death in adults. Although a few neurons survive after stroke, most neurons die due to ischemia. However, the involvement of nicotinic acetylcholine receptor signaling in the neuronal survival and death has not yet been fully elucidated. In addition, it has been reported that nicotine has a protective effect against ischemia-induced neural cell death, because ischemia-like oxygen-glucose deprivation (OGD) to mouse hippocampal slices increases neural cell death, but pretreatment of slices with nicotine decreases neural cell death (Neuroscience. 2007;145(3):866-72.). In this study, we explored cell death in mouse embryonic neocortex-derived primary cultured neurons that were subjected to OGD, and then treated with nicotine (an agonist) and/or mecamylamine (an antagonist).

   When nicotine was administered to primary cultured neurons immediately after 1 hour of OGD, cell death was suppressed. When nicotine was administered simultaneously with mecamylamine, there was a tendency for this suppression to be alleviated. Therefore, this showed that nicotinic acetylcholine receptor signaling is necessary to prevent neuronal cell death after ischemia-like OGD. Based on RNA sequencing, we also explored fold change in gene expression in administering nicotine or saline (control) to primary cultured neurons immediately after OGD. These results showed that nicotine treatment of primary cultured neurons after ischemic-like OGD increased the expression of transcription factor Npas4, as well as immediately early genes such as fosB and c-fos, and also enhanced the expression of Gem, a downstream factor of Npas4. Therefore, these results suggest that nicotinic acetylcholine receptor signaling may prevent neural cell death after ischemiclike OGD, perhaps via the Npas4-Gem pathway that we previously reported (PNAS. 2021;118(32):e2018850118.).