1. No.

   2023G010

2. Title

   Exploration and Elucidation of Novel Regulation Mechanism of Cellular Functions by Nicotine Focusing on Its Lipophilic Properties

3. Period

   2023-2025

4. Summary

We investigated the characteristics of the phenomenon where high-concentration nicotine (250 μM or higher) induces an increase in intracellular calcium in a nicotine receptor-independent manner, and our findings revealed the following:

- The calcium increase induced by high-concentration nicotine is observed in both the cytoplasm and the endoplasmic reticulum.
- Elevated intracellular calcium levels are caused by nicotine and its metabolites. Nicotine metabolites synergistically enhance the increase in calcium levels induced by nicotine.
- The increase in cytoplasmic calcium is caused by mobilization from intracellular calcium stores and influx from the extracellular space. Involvement of TRPC channels is suggested for the influx.
- Conversely, the origin of the increase in endoplasmic reticulum calcium is unclear, and the involvement of store-operated calcium entry has been probably ruled out.
- A similar phenomenon was observed in skin keratinocytes, which may be exposed to high concentrations of nicotine. This phenomenon may contribute to the efficient penetration of nicotine through the skin barrier and, consequently, to its penetration through the alveolar and blood-brain barriers.