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2. Title
   The Role of Ghrelin Regulation by Tobacco-Derived Chemicals on the Development of Nicotine Dependence

3. Period
   2023-2025

4. Summary
Ghrelin has been suggested to play a role in addictions, including nicotine addiction. However, it remains unclear whether tobacco-related chemicals impact ghrelin secretion. In this study, we assessed the direct effects of tobacco-related chemicals on ghrelin secretion using a newly developed ghrelin-secreting cell line, MGN3-1, expressing HiBiT-tagged ghrelin. This cell line enables the measurement of ghrelin levels via split-luciferase assay system. We found that nicotine and NNK-but not NO, propylene glycol, or menthol- tended to increase ghrelin secretion from MGN3-1 cells, which express α4β2 nicotinic acetylcholine receptors (nAChRs). An α4β2 nAChR-selective agonist, epibatidine, significantly stimulated ghrelin secretion, accompanied by a concurrent elevation in intracellular Na^+ and Ca^{2+} levels. The increase in intracellular Ca^{2+} levels was attenuated by the L-type Ca^{2+} channel inhibitor diltiazem. These results suggest that nicotine stimulates ghrelin secretion by activating α4β2 nAChR to induce membrane depolarization via Na^+ currents, which in turn elevate intracellular Ca^{2+} levels through voltage-gated Ca^{2+} channel in ghrelin cells.