Brief Report

DOI: 10.5582/ddt.2026.01034

Nicotine administration selectively inhibits kainate-induced *Arc* and *junB* but not *c-fos* and *egr1* mRNA expression in mouse cerebral cortex

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SUMMARY: The nicotinic acetylcholine receptor is an ion channel receptor that is highly expressed in the brain and can cooperatively propagate several signals with other ion channel receptors in neurons. However, little is known about how nicotinic acetylcholine and kainate receptors, both of which enable cation influx into neurons, cooperatively regulate immediate early genes. In this study, we administrated both ligands, nicotine and kainate, into mice and investigated alterations of the immediate early genes *activity-regulated cytoskeleton-associated protein* (*Arc*), *junB*, *c-fos*, and *egr1* in the cerebral cortex, hippocampus, olfactory bulb, and cerebellum. Kainate alone showed a tendency to induce all four immediate early genes in all four brain regions, whereas nicotine alone did not induce them strongly. However, pretreatment of nicotine before administration of kainate showed differential effects of nicotine on mRNA expression across different brain regions. Nicotine selectively inhibited kainate-induced *Arc* and *junB* mRNA expression in the cerebral cortex. These findings suggest that nicotine influences specific brain regions *via* the induction of certain immediate early genes.

Keywords: nicotine, kainate, *Arc*, *junB*, *egr1*, *c-fos*

1. Introduction

Nicotinic acetylcholine receptors (nAchRs) are enriched in the nervous system and play versatile roles in brain functions; as such, they may be promising therapeutic targets against brain disorders, including Alzheimer's disease (*1*). Two major nAchRs, composed of either α4β2 or α7 subunits, are predominantly expressed in the nervous system and act as ligand-gated ion channels with Ca^{2+} permeability (*1*). Besides these major subunits, several other nAchR subunits are distributed across different brain regions, probably resulting in diverse outputs for fine-tuning brain functions (*1*). The binding of nicotine or acetylcholine to nAchRs triggers depolarization and Ca^{2+} influx. This activates multiple intracellular signal transduction pathways that include phosphatidylinositol 3-kinase, protein kinase A, Ca^{2+}-calmodulin-dependent protein kinases, protein kinase C, or the subsequent extracellular signal-regulated mitogen-activated protein kinase (*1*), which might affect gene expression in cultured neuronal cells and animals (*2-4*). Previously, it has been reported that several immediate early genes (IEGs) are regulated by nicotine in PC12 cells (*2*) and *in vivo*, *e.g.*, in rodents (*3,4*). In particular, administration of nicotine to rats resulted in the induction of *c-fos* and *activity-regulated cytoskeleton-associated protein* (*Arc*) (*5*).

The kainate receptor is an ionotropic glutamate receptor and well-known ion channel that causes depolarization in neurons (*6*). It regulates the expression of several IEGs (*7,8*), inducing the expression of *junB, c-fos, egr1* (7), and *Arc* genes (*9*), and also evokes seizure (*10,11*) and neurotoxicity (*12,13*).

The activation of nAchRs protects against glutamate-mediated neurotoxicity (*14*), and nAchR-mediated neuroprotection has been observed in the hippocampus (*15,16*), striatum (*17,18*), and substantia nigra (*19,20*). The activation of nAchR propagates phosphatidylinositol 3-kinase-Akt signaling and suppresses amyloid-β-induced neuronal damage (*16,21*). The neuroprotective effects of nAchRs on kainate-induced excitotoxicity have also been reported by studies that administered both nicotine and kainate *in vivo* (*22-24*).

As described above, the effects of nAchRs on pathological phenomena triggered by the activation of glutamate receptors have mostly been demonstrated in relation to the suppression of excitotoxicity. However, little is known about the molecular mechanisms underlying the interactions of nAchRs with glutamate receptors. Both nAchRs and kainate receptors can regulate gene expression through downstream signaling

pathways. However, it remains unresolved how IEGs are regulated by the pretreatment of nAchRs before activation of kainate receptors. Thus, the current study investigated how representative IEGs (*i.e.*, *Arc*, *junB*, *c-fos*, and *egr1*) are differentially regulated in distinct brain regions by intraperitoneal administration of nicotine and kainate in mice.

2. Materials and Methods

2.1. Animals

C57BL/6N male 7-week-old mice were purchased from Japan SLC (Hamamatsu, Shizuoka, Japan). All animal experiments were performed in accordance with the ARRIVE guidelines and the requirements of the Animal Care and Experimentation Committee of the University of Toyama, Sugitani Campus (approval numbers A2022PHA-7 and A2025PHA-11). All efforts were made to minimize animal suffering and the number of animals used.

2.2. Reagents and treatments

(−)-Nicotine hydrogen tartrate (N5260) and kainic acid monohydrate (kainate) (K0250) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The mice were injected intraperitoneally with either saline (vehicle), 2 mg/kg nicotine dissolved in saline, or 30 mg/kg kainate dissolved in saline 2 h after nicotine administration. Animals were killed 30 min after kainate administration, and their brains were extracted.

2.3. RNA isolation and quantitative PCR (qPCR)

Total RNA was extracted from mouse brain tissues by the acid guanidine phenol-chloroform method. Total RNA was isolated by adding TRIsure (BIO-38032; Bioline, London, UK) to the tube with mouse brain and homogenizing the mixture with a polytron homogenizer (PT-2100, Kinematica AG, Malters, Switzerland), according to the manufacturer's instructions with minor modifications (*25*). After homogenization, total RNA was treated with RNase-free DNase I (TaKaRa, Shiga, Japan) to prevent contamination by genomic DNA. After the removal of DNase I, RNA (250 ng) was reverse-transcribed into cDNA using SuperScript II reverse transcriptase (Invitrogen), as previously described (*25*). To detect the mRNA levels of *Arc, junB, c-fos, egr1*, and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) genes, qPCR was performed in 20 µL of 1 × SYBR Select Master Mix (4472908, Thermo Fisher Scientific), 2 µL of cDNA solution, and 0.2 µM of each primer. The Stratagene Mx3000P or Mx3005P Real-Time PCR system was used, and the thermal profile was as follows: pre-heating at 50°C for 2 min followed by 95°C for 2 min, denaturation at 95°C for 15 s, annealing at 58°C for 15 s, and extension at 72°C for 1 min for 40 cycles. Standard curves were generated for each gene using a plasmid DNA dilution series containing the target sequences. The primer sequences are provided in the Supplementary material (Table S1, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=314*). Expression levels were normalized to *Gapdh* mRNA levels.

2.4. Statistical analysis

Data were presented as mean ± standard deviation (n = 3–4) and compared using two-way ANOVA or one-way ANOVA followed by a Tukey-Kramer or Scheffe *F* test. Differences were considered significant at $p < 0.05$. All statistical analyses were performed with Microsoft Excel 2013 (version 15.0.5127.1000).

3. Results and Discussion

A previous study already demonstrated that the IEGs, *Arc* and c-*fos* were activated in the rat brains by acute nicotine administration (*5*) and the previous study also suggest that these findings might be involved in nicotine-induced activation of the brain involved in stress and anxiety-linked behavior (*5*). On the other hand, it is reported that nicotine exerts the protective effect on kainate-induced neurotoxicity (*22-24*). These studies prompted us to investigate how IEGs are regulated by combinated treatment of nicotine and kainate to extend the previous study. To activate nAchRs prior to activation of kainate receptors in mice *in vivo*, we intraperitoneally administered their agonists: nicotine first and then kainate. Initially, we measured four IEGs (*Arc*, *junB*, *c-fos*, and *egr1*) by using RNAs isolated from cerebral cortices and qPCR. Nicotine alone did not significantly alter IEG expression; however, *Arc* and *junB* were slightly increased compared with the findings with the vehicle. Kainate alone significantly increased *Arc* and *junB* mRNA expression (Figures 1A and 1B). The expression of *c-fos and egr1* showed a slight increasing trend in the cerebral cortex stimulated with kainate (Figures 1C and 1D). Nicotine significantly inhibited the expression of *Arc* and *junB* but not *c-fos* and *egr1*, induced by kainate (Figures 1A–D).

Next, we assessed the expression of the four IEGs in the hippocampus (Figure 2). The expression of *c-fos* and *egr*1 was significantly induced by kainate alone (Figures 2C and 2D), and this increase was not decreased by the combined administration of nicotine and kainate (Figures 2C and 2D). Nicotine alone showed a tendency to decrease the expression of the four IEGs (Figures 2C and 2D). The expression of *Arc* and *junB* showed a slight increasing trend after kainate alone treatment; however, this increase was not significant and was not suppressed by nicotine (Figures 2A and 2B). Nicotine alone slightly decreased *junB* mRNA levels (Figure 2B).

In the olfactory bulb, kainate alone significantly

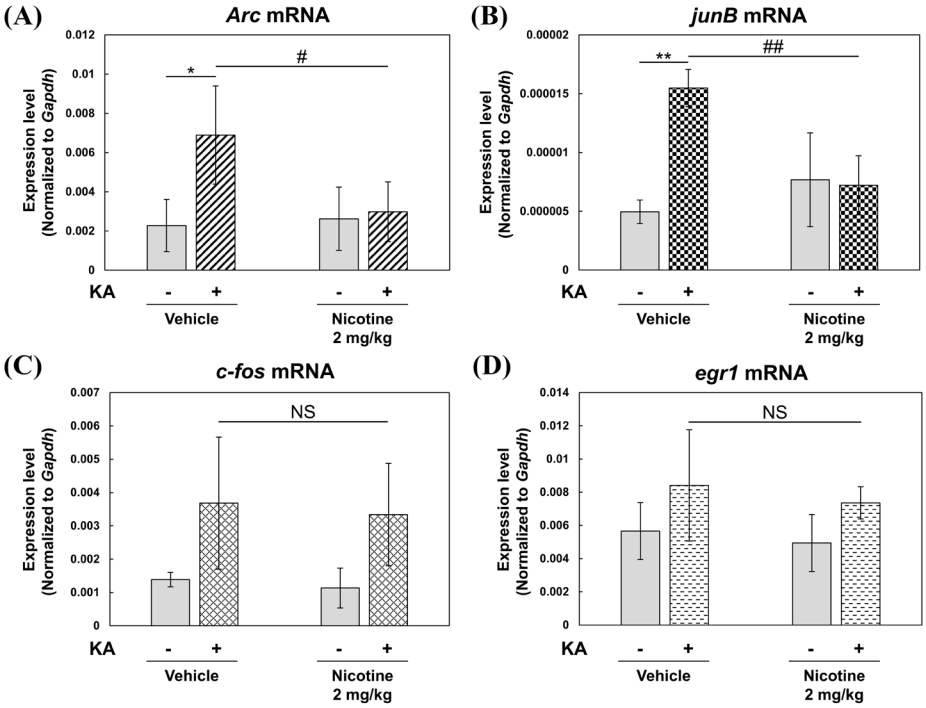

Figure 1. Kainate-induced *Arc* and *junB* mRNA levels are suppressed by nicotine administration in the cerebral cortex. Nicotine (2 mg/kg) and/or kainate (KA; 30 mg/kg) were administered into mice, and after 30 min, cerebral cortices were isolated, and total RNA was extracted and subjected to qPCR. (A–D) The mRNA expression levels of *Arc* (A), *junB* (B), *c-fos* (C), and *egr1* (D). Bars represent means ± SD (n = 3–4). Interactions between nicotine and kainate were analyzed using two-way ANOVA. *p = 0.0356 (A), **p = 0.00190 (B), p = 0.9420 (C) or p = 0.8766 (D). Differences were analyzed using one-way ANOVA with a post hoc Tukey-Kramer (A and B) or Scheffe F test (C). $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ *vs.* KA alone; NS, not significant *vs.* KA alone.

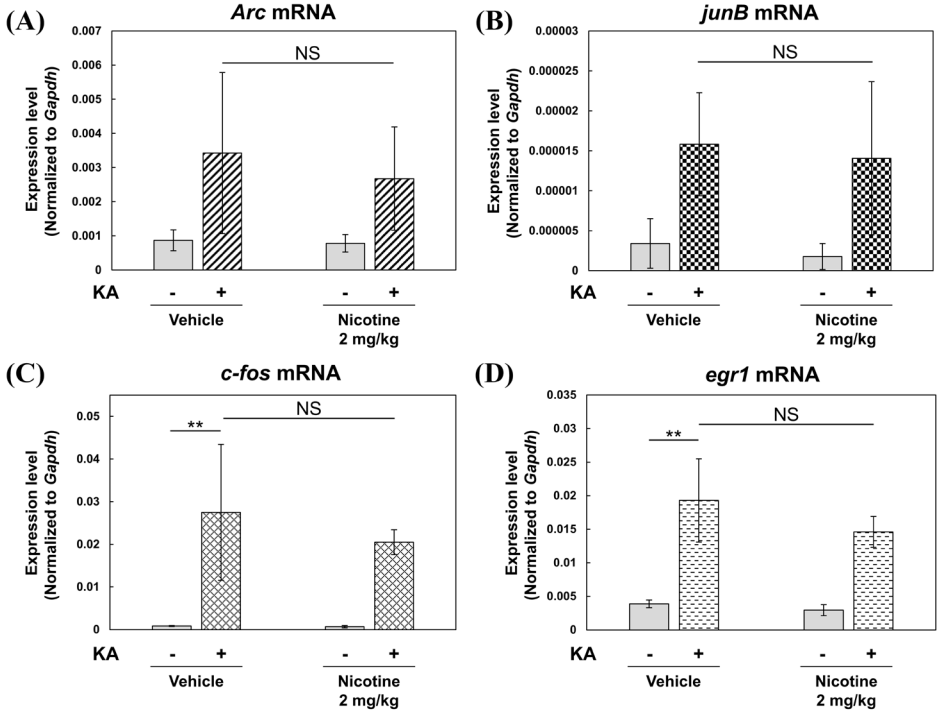

Figure 2. Kainate-induced *Arc*, *junB*, *c-fos*, and *egr1* mRNA levels are not suppressed by nicotine administration in the hippocampus. Nicotine (2 mg/kg) and/or kainate (KA; 30 mg/kg) were administered into mice, and after 30 min, hippocampi were isolated, and total RNA was extracted and subjected to qPCR. (A–D) The mRNA expression levels of *Arc* (A), *junB* (B), *c-fos* (C), and *egr1* (D). The bars represent means ± SD (n = 4). Interactions between nicotine and kainate were analyzed using two-way ANOVA. p = 0.6486 (A), p = 0.9834 (B), p = 0.4158 (C) or p = 0.2836 (D). Differences were analyzed using one-way ANOVA with a post hoc Tukey-Kramer (B) or Scheffe F test (C and D). $^{**}p < 0.01$ *vs*. control; NS, not significant *vs*. KA alone.

increased *junB* mRNA expression (Figure 3B) and showed a tendency to increase *Arc*, *c-fos*, and *egr*1 (Figures 3A, 3C, and 3D). Nicotine alone showed a tendency to decrease *junB* mRNA expression (Figure 3B).

In the cerebellum, kainate alone significantly increased *Arc*, *c-fos*, and *egr1* expression and showed a tendency to increase *junB* expression (Figures 4A–4D). Although the interaction between nicotine and kainate was observed in terms of *Arc* expression (Figure 4A, figure legend), post hoc test in kainate alone versus kainate plus nicotine did not show significant difference. Nicotine suppressed the kainate-induced increases in *c-fos* expression (Figure 4C).

In summary, nicotine differentially affected *Arc*, *junB*, *c-fos*, and *egr1* expression levels, also across different brain regions. In the case of combined administration of nicotine prior to kainate treatment, nicotine exerted an inhibitory effect on kainate-induced IEG mRNA expression. Excitatory neuronal activation is also induced by kainate, associated with seizure (*10,11*). Previously, the inhibitory effect of nicotine on kainate-induced wet dog shakes followed by motoric seizure has been reported (*23*). Taken together, therefore, the suppressive effect of nicotine on some of IEG expression may be due to the reduction of seizure. Notably, this suppressive effect of nicotine was not observed for all IEGs and in all brain regions. This indicates selective suppression, depending on the IEG and/or brain region. Especially in the cerebral cortex, nicotine selectively and strongly blocked kainate-induced *Arc* and *junB* mRNA expression.

The subunits of nAchRs have been reported to be spatiotemporally expressed in the central nervous system (*1,26*). The cerebral cortex expresses the subunits α2, α4, α5, and α7, and the hippocampus expresses these same subunits in addition to α3 (*1*). The cerebellum expresses the subunits α3, α4, and α7 (*1*). Thus, differential expression patterns of nAchR subunits across different brain regions might result in distinct nAchR channel properties in each brain region, further leading to different activation of downstream signaling and gene expression. In this study, we used 7-week-old mice to evaluate the effects of nicotine and kainate on IEG expression. Notably, nAchR subunit and thus channel variability during brain development may also play critical roles in physiological and pathological processes in the brain (*26*). Therefore, further studies are needed to investigate whether our findings can also be applied to neonatal or aged brain and whether alterations in IEG expression based on interactions between nAchRs and kainate receptors contribute to brain development and higher brain functions, such as learning and memory.

The molecular mechanisms by which nicotine inhibits kainate-induced IEG expression remain unknown. The neuroprotective role of nicotine against glutamate toxicity and the underlying mechanisms, which include

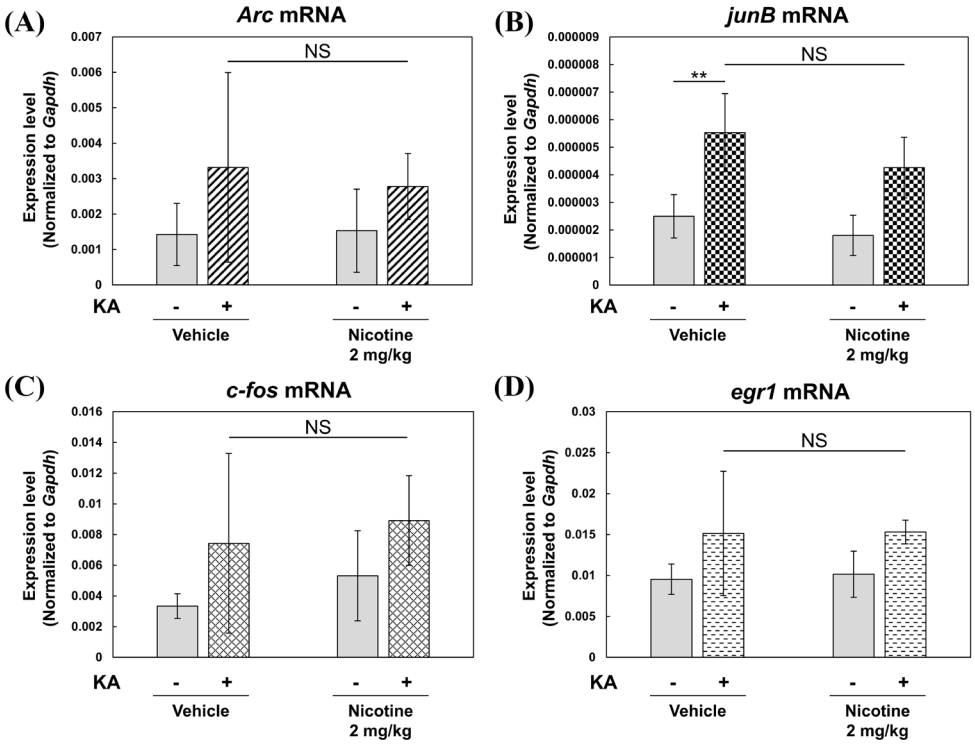

Figure 3. Kainate-induced *junB* mRNA levels are not significantly suppressed by nicotine administration, and nicotine alone tends to decrease *junB* mRNA levels in the olfactory bulb. Nicotine (2 mg/kg) and/or kainate (KA; 30 mg/kg) were administered into mice, and after 30 min, olfactory bulbs were isolated, and total RNA was extracted and subjected to qPCR. (A–D) The mRNA expression levels of *Arc* (A), *junB* (B), *c-fos* (C), and *egr1* (D). The bars represent means ± SD (n = 3–4). Interactions between nicotine and kainate were analyzed using two-way ANOVA. $p = 0.6926$ (A), $p = 0.6164$ (B), $p = 0.8943$ (C) or $p = 0.9188$ (D). Differences were analyzed using one-way ANOVA with a post hoc Tukey-Kramer (B). $^{**}p < 0.01$ *vs.* control; NS, not significant *vs.* KA alone.

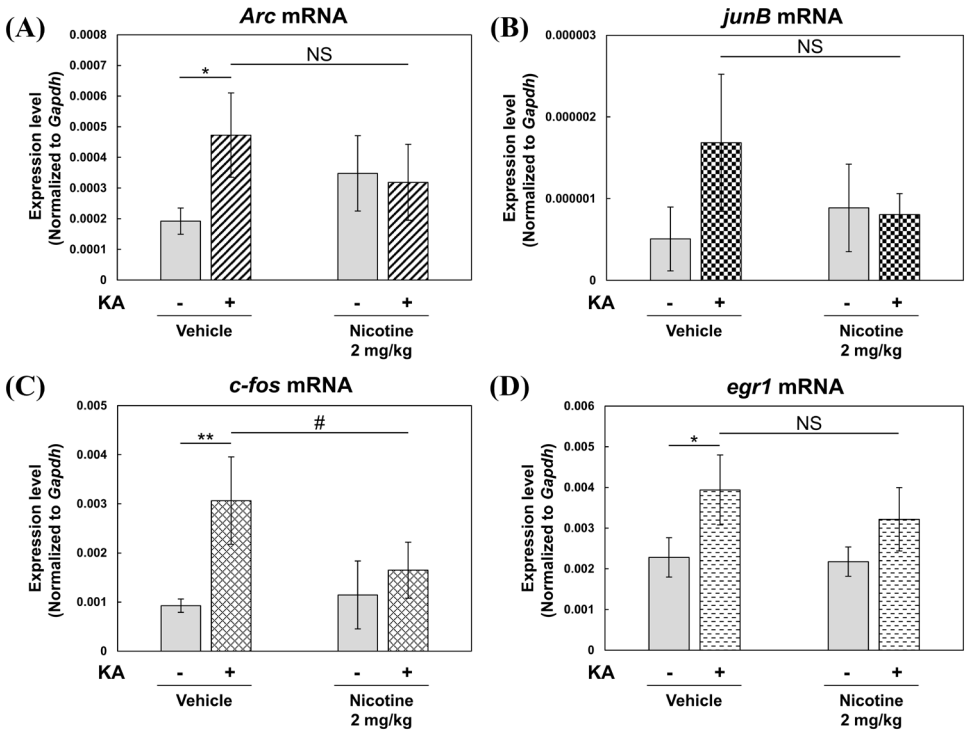

Figure 4. Kainate induces *Arc*, *c-fos*, and *egr1* mRNA expression, and kainate-induced *c-fos* mRNA expression is suppressed by nicotine in the cerebellum. Nicotine (2 mg/kg) and/or kainate (KA; 30 mg/kg) were administered into mice, and after 30 min, cerebelli were isolated, and total RNA was extracted and subjected to qPCR. (A–D) The mRNA expression levels of *Arc* (A), *junB* (B), *c-fos* (C), and *egr1* (D). The bars represent means ± SD (n = 3–4). Interactions between nicotine and kainate were analyzed using two-way ANOVA. $^{*}p = 0.0180$ (A), $p = 0.0542$ (B), $^{*}p = 0.0245$ (C) or $p = 0.3633$ (D). Differences were analyzed using one-way ANOVA with a post hoc Tukey-Kramer test. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* control; $^{\#}p < 0.05$ *vs*. KA alone; NS, not significant *vs*. KA alone.

the phosphatidylinositol 3-kinase-Akt pathway (*21*) and non-neuronal cells such as microglia (*27,28*), might provide critical insights into the underlying mechanisms of the findings of this study. Among the affected IEGs, *Arc* and *junB* were particularly more sensitive to nicotine treatment in the cerebral cortex (Figure 1). This finding suggests that nicotine may block specific transcription factors or posttranscriptional events, which commonly and selectively drive *Arc* and *junB* gene expression. Serum response factor is one of the common transcription factors that regulate both *Arc* and *junB* genes (*29,30*), implying that, together with its regulatory complexes, it might be affected by nicotine and kainate in the cerebral cortex. In the present study, however, we did not take pharmacological or genetic approaches to elucidate the mechanisms as proposed above. Therefore, this study has limitations to fully explain the involvement of differential nAchRs subunits at differential brain regions and SRF transcriptional factor complex. To further address this molecular mechanism, investigations into the subcellular localization and posttranslational modification of specific transcription factor proteins *in vivo* are warranted.

A growing body of evidence is accumulating that shows that nAchRs and their ligands may be involved in brain health and diseases and represent therapeutic targets for neurodegenerative diseases (*1,26*). Studies on the effects of nicotine on gene expression should lead to a deeper understanding of the roles of nicotine and ultimately contribute to the development of novel therapeutic strategies for brain diseases.

Acknowledgements

This study was supported by the Smoking Research Foundation (to A.T.). The funder did not have any role in the study design, data collection or analysis, manuscript preparation, or the decision to submit the manuscript for publication. We thank Dr. Eva Lasic, PhD, from Edanz (*https://jp.edanz.com/ac*), for editing a draft of this manuscript.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received May 19, 2026; Revised July 28, 2026; Accepted August 12, 2026.

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Released online in J-STAGE as advance publication August 21, 2026.