Co-activation of nAChR and mGluR induces γ oscillation in rat medial septum diagonal band of Broca slices

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Aim: To examine whether co-activation of nAChR and mGluR1 induced γ oscillation (20–60 Hz) in rat medial septum diagonal band of Broca (MSDB) slices.

Methods: Rat brain sagittal slices containing the MSDB were prepared. Extracellular field potentials were recorded with glass microelectrodes. The nAChR and mGluR1 agonists were applied to the slices to induce network activity. Data analysis was performed off-line using software Spike 2.

Results: Co-application of the nAChR agonist nicotine (1 µmol/L) and the mGluR1 agonist dihydroxyphenylglycine (DHPG, 25 µmol/L) was able to induce γ oscillation in MSDB slices. The intensity of nAChR and mGluR1 activation was critical for induction of network oscillation at a low (θ oscillation) or high frequency (γ oscillation): co-application of low concentrations of the two agonists only increased the power and frequency of oscillation within the range of θ, whereas γ oscillation mostly appeared when high concentrations of the two agonists were applied.

Conclusion: Activation of mGluR1 and nAChR is able to program slow or fast network oscillation by altering the intensity of receptor activation, which may provide a mechanism for modulation of learning and memory.

Keywords: nAChR; mGluR1; DHPG; nicotine; θ oscillation; γ oscillation; the medial septum diagonal band of Broca; learning and memory

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Introduction

Hippocampal rhythmic activity[1] in the θ (4–12 Hz) and γ (20–60 Hz) frequency bands have received considerable interest as they are presumed to play important roles in many brain functions, such as spike-timing-dependent synaptic plasticity, sensory information processing and memory processes[2, 3]. It is well-established that the cholinergic and GABAergic neurons located in the medial septum-diagonal band complex (MSDB) project to the hippocampus and contribute to the generation of the hippocampal θ rhythm[4, 5] and memory formation[6]. Glutamatergic neurons in the MSDB[7] provide powerful excitatory inputs to cholinergic and GABAergic neurons via activation of either metabotropic glutamate receptors (mGluRs) or ionotropic glutamate receptors[8, 9].

Activation of either mGluR1 or kainite receptor induced γ oscillations in hippocampal slices[10, 11], but it only induced θ oscillations in MSDB slices[12, 13], suggesting that the local circuit of the neuronal network for the generation of rhythmic activity between the hippocampus and the MSDB are different.

Several lines of evidence indicate that nicotinic acetylcholine receptors (nAChRs) are highly expressed in the MSDB and hippocampus[13, 14]. Nicotine induced θ oscillations in the MSDB and in the hippocampus[15-17], suggesting that nAChR activation modulates septal-hippocampal function[18].

Network oscillation represents physiological information processing and is altered in pathological process. Recent studies indicate that patients with schizophrenia, a common disease involving disordered information processing, showed impairment in evoked γ oscillations[19]. Cigarette smoking is
significantly more prevalent in individuals with schizophrenia than in normal individuals, suggesting that nicotine may alleviate neurocognitive symptoms associated with this disorder.

In this study, we found that the activation of either nAChR or mGluR1 alone only induced network oscillations in the θ range with limited synchronization in MSDB slices, but co-activation of mGluR1 and nAChR was able to induce highly synchronized γ oscillations. The induction of γ oscillations in the MSDB is likely to have an impact on the cognitive function of the septal-hippocampal system.

Materials and methods
Preparation of slices
All procedures were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986 and the associated guidelines and with prior approval from the local ethical committee of the University of Leeds, UK and the Medical University of Xinxing, Xinxian, China. All efforts were made to minimize animal suffering and to reduce the number of animals used. Male Wistar rats (3 weeks old, n=50) were anaesthetized by intraperitoneal injection of Sagatal (sodium pentobarbitone, 100 mg/kg, Rhône Mérieux Ltd, Harlow, UK). When all pedal reflexes were abolished, the animals were perfused intracardially with chilled (5°C), oxygenated artificial cerebrospinal fluid (ACSF) in which the sodium chloride had been replaced by iso-osmotic sucrose. This ACSF (305 mmol/L) contained the following (in mmol/L): 225 sucrose, 3 KCl, 1.25 NaHPO₄, 24 NaHCO₃, 6 MgSO₄, 0.5 CaCl₂, and 10 glucose. For extracellular field recording, two sagittal slices (450 μm) of rat brain, straddling the midline and containing the MSDB were cut at 4–5 °C in the sucrose ACSF using a Leica VT1000S vibratome (Leica Microsystems UK, Milton Keynes, UK).

Electrophysiological recording and data analysis
For the extracellular field potential recordings, two MSDB slices were transferred to an interface recording chamber. The slices were maintained at a temperature of 33°C, and ACSF and humidified carbogen gas (95% O₂–5% CO₂) were applied at the interface. The ACSF contained the following (in mmol/L): 126 NaCl, 3 KCl, 1.25 NaHPO₄, 24 NaHCO₃, 2 MgSO₄, 2 CaCl₂, and 10 glucose. The slices were allowed to equilibrate in this medium for 1 h prior to recording. Both channels of an Axoprobe 1A amplifier (Axon Instruments, Union City, CA, USA) were employed for the extracellular field recordings, which were conducted using glass microelectrodes containing ACSF (resistance 2–5 MΩ). The data were band-pass filtered online between 0.5 Hz and 2 kHz using the Axoprobe amplifier and a Neurolog system NL106 AC/DC amplifier (Digitimer Ltd, Welwyn Garden City, UK). The data were digitized at a sample rate of 5–10 kHz using a CED 1401 plus ADC board (Digitimer Ltd). Electrical interference from the main supply was eliminated from the extracellular recordings online with the use of 50-Hz noise eliminators (HumBug, Digitimer Ltd, North Vancouver, Canada).

The data were analyzed off-line using software from Spike 2 (CED, Cambridge, UK). Power spectra were generated to provide a quantitative measure of the frequency components in a stretch of recording, where power, a quantitative measure of the oscillation strength, was plotted against the respective frequency. Power spectra were constructed for 30- to 60-s epochs of extracellular field recordings using a fast Fourier transform algorithm provided by Spike 2. The parameters used for measuring the oscillatory activity in the slices were the peak frequency (Hz) and the area power (μV²). In the current study, the area power was equivalent to the computed area under the power spectrum between the frequencies of 20 and 60 Hz.

Statistical analysis
All statistical tests were performed using SigmaStat software (SPSS Inc, St Louis, CA, USA). The results are expressed as the mean±standard error. Statistical significance for comparison between the two groups was determined with Student’s t-test or a rank sum test. Statistical comparisons for more than two groups were made using either a one-way analysis of variance (ANOVA) or an ANOVA on ranks or repeated measures (RM) ANOVA. P<0.05 was considered statistically significant.

Results
Pretreatment of MSDB slices with nicotine followed by DHPG induced γ oscillations
Bath application of nicotine (1 μmol/L) followed by DHPG (25 μmol/L) induced fast network oscillation in the γ frequency band (Figure 1). The oscillatory activity was not observed in the control condition, but a slow oscillatory event (6 Hz) with a relatively small power was observed after the application of nicotine, and a fast oscillatory event (36 Hz) with a large power was induced after the application of DHPG (Figure 1A, 1B). The autocorrelograms showed that there was obvious autocorrelation for nicotine- or nicotine plus DHPG-induced oscillation, but there was no obvious correlation for the control (Figure 1C). On average, nicotine alone induced an oscillation in the θ frequency band (7.3±0.5 Hz, n=7). Compared with the control (5.5±0.6 Hz), there was a statistically significant difference (P<0.05). Nicotine plus DHPG induced a fast network oscillation in the γ frequency band (29.8±2.7 Hz, n=7). Compared with the control and nicotine treatment alone, there was a statistically significant difference (P<0.001) (Figure 1D).
The changes of power for the dominant oscillatory events are shown in a bar graph (Figure 1E). The average peak power was 2.4±0.6, 9.5±3.3, and 33.8±9.5 µV² for the control, nicotine and nicotine+DHPG treatments, respectively (n=7 for all groups); there were statistically significant differences between the control and nicotine groups (P<0.05), the control and nicotine+DHPG groups (P<0.05) and the nicotine alone and nicotine+DHPG groups (P<0.05).

We tested the effects of an α7 nAChR antagonist, methyllycaconitine (MLA), and a non-α7 nAChR antagonist, DhβE, on the γ oscillation induced by nicotine+DHPG. In the presence of MLA (Figure 2A), nicotine induced θ oscillation in some slices (Figure 2A1, 2A2), although no statistically significant difference was found. Co-application of nicotine+DHPG was able to induce a large θ oscillation and minor oscillatory events in the γ frequency band (Figure 2A1, 2A2). The peak frequencies were 1.9±0.7, 4.1±2.0, 4.8±1.9, and 5.3±2.3 Hz for the control, MLA, MLA+nicotine, and MLA+nicotine+DHPG treatments, respectively. There was a statistically significant difference between the control and the MLA+nicotine+DHPG group (P<0.05, n=7).

In the presence of DhβE, nicotine was not able to induce obvious oscillatory activity, but co-application of nicotine+DHPG induced θ oscillation in some slices, although no statistically significant difference existed among these groups (P>0.05, n=6). The peak powers were 7.5±3.4, 6.0±2.5, 6.3±1.5, and 11.0±4.7 µV² for the control, DhβE, DhβE+nicotine, and DhβE+nicotine+DHPG treatments, respectively. There were no statistically significant differences among these groups (P>0.05, n=6).

In the condition of MLA+DhβE, neither nicotine alone nor nicotine+DHPG induced detectable oscillatory activity (Figure 2C). The average peak frequencies were 1.9±1.0, 1.9±0.0, 2.6±1.7, and 2.9±0.6 Hz for the control, MLA+DhβE, MLA+DhβE+nicotine, and MLA+DhβE+nicotine+DHPG treatments, respectively. There were no statistically sig-
significant differences among these groups ($P>0.05, n=4$). The peak powers were 4.4±2.0, 15.6±13.1, 7.1±4.9, and 11.9±10.5 µV$^2$ for the control, MLA+DhβE, MLA+DhβE+nicotine, and MLA+DhβE+nicotine+DHPG treatments, respectively. There were no statistically significant differences among these groups ($P>0.05, n=4$).

In some cases ($n=2$ of 5), nicotine (1 µmol/L) did not induce detectable oscillatory activity, and further application of 25 µmol/L DHPG was still able to induce γ oscillations (Figure 3A, 3B), indicating that θ oscillation is not a requirement for the induction of γ oscillation. The time course of the area power changes of the γ oscillations (γ power, which is the area power for the oscillatory events of 20–60 Hz) is shown in Figure 3C. Nicotine (1 µmol/L) did not alter the power in the basal condition. Further application of DHPG dramatically increased the area power, and this increase reached a plateau (~300 µV$^2$) at 50 min after DHPG application. To further confirm that the oscillatory events were indeed biological signals, we applied the antagonists of the ionotropic glutamate receptors AP5 and NBQX to MSDB slices and found that the γ power induced by DHPG plus nicotine was largely reduced by these glutamate receptor antagonists, suggesting that γ...
tested the effects of bicuculline, a GABA$_A$ receptor antagonist, on the $\gamma$ oscillation induced by nicotine+DHPG. Figure 3D shows that the nicotine+DHPG-induced $\gamma$ oscillation was largely reduced by 20 $\mu$mol/L bicuculline.

**Pretreatment with DHPG followed by nicotine induced $\theta$ and $\gamma$ oscillations**

A series of experiments were performed in which DHPG (25 $\mu$mol/L) was applied to MSDB slices first, followed by the application of nicotine (1 $\mu$mol/L). A representative experiment is shown in Figure 4. There was no oscillatory activity in the control condition. DHPG induced small oscillatory events without a clear dominant frequency (Figure 4Aa, 4Ab); additional application of nicotine induced large oscillatory activity with a clear dominant frequency (35 Hz) in the $\gamma$ band (Figure 4Ab).

In general, DHPG (25 $\mu$mol/L) induced a single event at the $\theta$ frequency. In the case of multiple events, only the oscillatory event at the highest power was chosen for the average. As shown in Figure 4Ac, DHPG induced an oscillation in the $\theta$ frequency band (12.3±2.4 Hz, $n=6$). Compared with the control (6.8±0.5 Hz, $n=6$), there was a significant increase in the oscillatory frequency after DHPG ($P<0.05$). After a steady state (20 min after DHPG addition) was reached, further application of nicotine induced a fast network oscillation in the $\gamma$ frequency band (27.1±1.9 Hz, $n=6$). There were statistically significant differences between the control and DHPG+nicotine groups ($P<0.001$) and between the DHPG and DHPG+nicotine groups ($P<0.01$). The changes of power for the dominant oscillatory events are shown in a bar graph (Figure 4Ad). The average peak power was 2.9±1.3, 9.5±2.5, and 22.0±5.9 $\mu$V$^2$ for the control, DHPG and DHPG+nicotine treatments, respectively ($n=6$ for all groups); there were statistically significant differences between the control and the DHPG group ($P<0.05$), the control and the DHPG+nicotine group ($P<0.05$) and the DHPG alone group and the DHPG+nicotine group ($P<0.05$).

To test whether a combination of a low dose of DHPG (3 $\mu$mol/L) plus micromolar concentrations of nicotine would be able to induce a fast network oscillation, we applied DHPG (3 $\mu$mol/L) first to MSDB slices. No obvious oscillatory activity was observed; however, further application of nicotine (1 $\mu$mol/L) induced oscillatory activity in the $\gamma$ frequency band ($n=3$ out of 5, Figure 4Ba, 4Bb).

**Low doses of DHPG and nicotine did not induce fast $\gamma$ oscillation, but did induce $\theta$ activity**

Figure 5A and B show that a low concentration of DHPG (3 $\mu$mol/L) alone did not induce oscillatory activity. Further application of a low concentration of nicotine (25 $\mu$mol/L) induced no obvious fast oscillations, but slow oscillatory activities in the $\theta$ range (8.5 Hz) were observed as well as an oscillation event in $\beta$ range (15 Hz) (Figure 5B).

On average, 3 $\mu$mol/L DHPG alone induced an oscillation in the $\theta$ frequency band (6.9±0.5 Hz, $n=8$, Figure 5C). Compared with the control (5.5±0.4 Hz, $n=8$), there was a signifi-
cant increase in the oscillatory frequency ($P<0.01$). When a steady state (20 min following DHPG) was reached, further application of nicotine (25 nmol/L) induced oscillation at a higher frequency, but it was still within the $\theta$ range ($8.5\pm0.6$ Hz, $n=8$). There were statistically significant differences in the oscillatory frequency between the control and DHPG+nicotine groups ($P<0.001$) and the nicotine and DHPG+nicotine groups ($P<0.01$). The average peak power was $2.8\pm0.7$, $5.4\pm1.0$, and $10.4\pm1.4$ $\mu$V$^2$ for the control, DHPG, and DHPG+nicotine treatments, respectively ($n=8$ for all the groups); there were statistically significant differences between the control and DHPG groups ($P<0.001$), the control and DHPG+nicotine groups

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**Figure 4.** Pretreatment of MSDB slices with DHPG followed by nicotine induced network activity. (Aa) Field potential recordings (1-s epoch) of persistent network oscillations are shown under control conditions (upper panel), after bath-applied DHPG (25 $\mu$mol/L) (middle panel) and after DHPG (25 $\mu$mol/L)+nicotine (1 $\mu$mol/L) application (lower panel). Ab: The power spectra showed no detectable oscillatory activity (black line) in the control condition. Multiple small peaks of oscillatory events (4.9, 15, and 23 Hz) were observed after bath-applied DHPG (25 $\mu$mol/L) (blue line), and a large peak (35 Hz) of oscillatory was observed after DHPG (25 $\mu$mol/L)+nicotine (1 $\mu$mol/L) application (red line). (Ac) Bar graph summarized the changes in the peak frequency of oscillation in the control conditions and after DHPG and DHPG+nicotine application. (Ad) Bar graph summarizing the changes in the peak power of oscillation in the control and during DHPG and DHPG+nicotine application. (Ba) Field potential recordings (1-s epoch) of persistent network oscillations are shown under control conditions (upper panel), after DHPG (3 $\mu$mol/L) application (middle panel) and after DHPG (3 $\mu$mol/L)+nicotine (1 $\mu$mol/L) application (lower panel). (Bb) The corresponding power spectra demonstrate a dominant oscillatory activity in the $\gamma$ frequency band (40 Hz) after application of DHPG+nicotine (red line). There was no apparent oscillatory activity under control conditions or after the application of DHPG. $^bP<0.05$, $^cP<0.01$ vs control. $^eP<0.05$, $^fP<0.01$ vs DHPG alone.
Conversely, application of 25 nmol/L nicotine alone induced a small θ oscillation (8.7 Hz), and further application of 3 µmol/L DHPG increased occasionally the oscillatory power and frequency (12 Hz) (Figure 6A, 6B). On average, 25 nmol/L nicotine alone induced a θ oscillation (6.9±0.8 Hz, n=5). Compared with the control (4.7±0.4 Hz, n=5), there was no statistically significant difference in the oscillatory frequency. After a steady state (20 min following nicotine) was reached, further application of DHPG (3 µmol/L) induced a θ oscillation at a higher frequency (9.9±1.5 Hz, n=5). There were statistically significant differences between the control and nicotine+DHPG groups (P<0.05) and between the nicotine and nicotine+DHPG groups (P<0.05). The changes of power for the dominant oscillatory activity are shown in a bar graph (Figure 6D). The average peak power was 3.2±1.2, 8.4±1.1, and 12.0±1.1 µV² for the control, nicotine and nicotine + DHPG treatments, respectively (n=5 for all groups). There were statistically significant differences between the control and nicotine groups (P<0.05) and the control and the nicotine+DHPG groups (P<0.01); there was no statistically significant difference between the nicotine alone and the nicotine+DHPG groups in peak power (P>0.05).

Discussion

The present study extends our previous investigations\[15, 16, 22\] on the contribution of nAChR and mGluR1 to the control of θ and γ oscillations in the MSDB. Specifically, we demonstrated that co-activation of mGluR1 and nAChR can control the pattern of network oscillation in MSDB through the combination of various concentrations of two receptor agonists, DHPG and nicotine.

Previous studies demonstrate that nAChR is expressed in both glutamatergic and GABAergic neurons within the local network circuit of MSDB\[23, 24\], suggesting that activation of these receptors may alter MSDB function. DHPG (10 µmol/L) induced synchronous γ oscillation in hippocampus which are driven by the complex network of the CA3 region (rich in recurrent collateral connection) involving both excitatory and inhibitory synaptic transmission\[25\]. In this study, DHPG (25 µmol/L) failed to induce γ oscillation in the MSDB, suggesting that the neuronal arrangement of the local network circuits between the two structures is different.

Nicotine alone was not able to induce γ oscillation in the hippocampus at a concentration 1 µmol/L, although nicotine increased the power of the evoked transient γ oscillation\[17\]. The enhancement of evoked hippocampal γ oscillations by nicotine can be reduced by α7 nAChR antagonists, which is...
in agreement with our observation in the hippocampus that nicotine-induced θ oscillations can be reduced by α7 nAChRs antagonists[16]. In the MSDB, nicotine-induced θ oscillation can be reduced by α4 but not α7 nAChR antagonists[24]. Thus, it appears that α7 nAChRs play a role in nicotine-mediated enhancement of hippocampal-related functions and that non-α7 nAChRs are involved in the modulation of MSDB-related functions.

At a low concentration, neither nicotine (25 nmol/L) nor DHPG (3 µmol/L) was able to induce fast γ oscillation. Combination of the two receptor agonists enhanced the oscillatory power and frequency, but the frequency was limited to the θ range (14 Hz), suggesting that the weak activation of nAChR and mGluR1 is not able to induce fast network oscillation. Although nicotine (1 µmol/L) or DHPG (25 µmol/L) alone was not able to induce fast network oscillation on its own, the combination of these two agents induced γ oscillation. Our results indicate that in the presence of DhβE but not MLA, nicotine+DHPG failed to induce γ oscillation, suggesting that α4β2 nAChR plays a more important role than α7 nAChR in mediating the oscillatory activity of MSDB, which is in line with our previous observation that α4β2 nAChR mediated nicotine-induced θ activity in the MSDB[24]. Our results further demonstrated that the induced γ oscillation is dependent on excitatory and inhibitory neurotransmission based on the roles of AMPA receptor and GABAA receptor blockers, which is in agreement with previous reports[26, 27].

Preview studies suggest that the induction of hippocampal γ and θ oscillations relies on the firing pattern of inhibitory neurons. γ oscillation is associated with the activation of fast-firing basket cell inhibitory interneurons[26, 29] that act on fast GABAa receptors[30–32], whereas, θ oscillation involves slow stellate cell inhibitory interneurons[33] that act on slow GABAa receptors[30]. Our results suggest that the γ oscillation induced by nicotine and DHPG may be involved in the activation of the fast firing inhibitory interneuron in the MSDB.

In this study, we confirmed that nicotine can increase the synchronization of network oscillation in MSDB slices. Our result was supported by the analysis of computer modeling, which showed that nicotine reduced the complexity of network activity, suggesting that nicotine increase synchronized neural firing[34].

In vivo studies have demonstrated that nicotine increases the auditory stimulus-evoked γ oscillations[35]. Smokers also exhibited enlarged auditory stimulus-evoked γ oscillations in the cortex. These studies suggest that nicotine can enhance cortical activation and sensory information processing[36]. γ oscillation induced in the MSDB in vitro may drive fast hippocampal oscillation and have an impact on hippocampal-dependent learning and memory. Given that γ oscillations are indices of sensory information processing that are altered or disrupted in disorders such as Alzheimer’s disease and schizo-
phrenia[19], nicotine may be beneficial to individuals with these diseases.

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Author contribution

Ya-li WANG performed the experiments, analyzed the data and wrote the paper; Jian-gang WANG analyzed the data; Gao-xiang OU-YANG analyzed the data; Xiao-li LI analyzed the data; Z HENDERSON designed the research; Cheng-biao LU designed the experiments, performed the experiments and wrote the paper.

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