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Research report

Effects of acute nicotine on prepulse inhibition of auditory change-related cortical responses

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HIGHLIGHTS

- Effects of acute nicotine on PPI of Change-N1m were studied using MEG.
- Nicotine tended to enhance Change-N1m and significantly enhanced PPI of Change-N1m.
- The enhancing effect of nicotine on PPI of Change-N1m was similar to that on PPI of startle.
- PPI of Change-N1m and PPI of startle share at least some common mechanisms.

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ABSTRACT

Prepulse inhibition (PPI) of startle is a measure of inhibitory function in which a weak leading stimulus suppresses the startle response to an intense stimulus. Usually, startle blink reflexes to an intense sound are used for measuring PPI. A recent magnetoencephalographic study showed that a similar phenomenon is observed for auditory change-related cortical response (Change-N1m) to an abrupt change in sound features. It has been well established that nicotine enhances PPI of startle. Therefore, in the present magnetoencephalographic study, the effects of acute nicotine on PPI of the Change-N1m were studied in 12 healthy subjects (two females and 10 males) under a repeated measures and placebo-controlled design. Nicotine (4 mg) was given as nicotine gum. The test Change-N1m response was elicited with an abrupt increase in sound pressure by 6 dB in a continuous background sound of 65 dB. PPI was produced by an insertion of a prepulse with a 3-dB-louder or 6-dB-weaker sound pressure than the background 75 ms before the test stimulus. Results show that nicotine tended to enhance the test Change-N1m response and significantly enhanced PPI for both prepulses. Therefore, nicotine's enhancing effect on PPI of the Change-N1m was similar to that on PPI of the startle. The present results suggest that the two measures share at least some mechanisms.

1. Introduction

When a sudden and intense sensory stimulus is presented, automatic contraction of facial or skeletal muscle occurs. This reflexive response is called the startle reflex. The startle reflex is considered as a component of the defense reaction [1]. Prepulse inhibition (PPI) is a phenomenon whereby a startle reflex is suppressed when a weak stimulus (prepulse) precedes the startling stimulus [2]. PPI is considered as a measure of an inhibitory process in which irrelevant sensory information is screened out so that an individual can focus on the most salient events in the sensory environment [for reviews, see Refs. 3–5]. In humans, PPI is usually observed by using blink reflexes following an intense sound. PPI is an important tool to understand the biology of schizophrenia because it has been established that PPI is impaired in schizophrenics [6–9] and unaffected first-degree relatives of probands [10,11]. Animal models of impaired PPI are used for the evaluation of antipsychotic drugs [for review, see Ref. 12].

Nicotine or cigarette smoking enhances PPI of the acoustic startle in healthy smokers and non-smokers [13–16], and

Abbreviations: ANOVA, analysis of variance; BESA, brain electric source analysis; Change-N1m, change-related auditory N1m; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; mAChR, muscarinic acetylcholine receptor; nAChR, nicotinic acetylcholine receptor; PPI, prepulse inhibition; Pre, pre-nicotine/placebo administration; Post, post-nicotine/placebo administration; SQUID, superconducting quantum interference device.

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transiently improves acoustic PPI in patients with schizophrenia [17–19]. The enhancing effect of nicotine has also been demonstrated in animals [20,21]. Similar to PPI, acoustic P50 gating, another measure of the inhibitory process, is impaired in patients with schizophrenia [22,23] and nicotine improves the reduced P50 gating in schizophrenics [24] and their first-degree relatives [25]. These findings indicate that nicotine is involved in the inhibitory process and that impaired inhibitory function may contribute to symptoms of schizophrenia or its association with a high prevalence of smoking behavior [26].

Change-related cortical responses are a sensory-evoked cortical activation specific to a change of stimulus in the auditory [27–33], somatosensory [34–37], and visual [38–40] systems. The change-related cortical response is recorded very clearly using electroencephalography (EEG) or magnetoencephalography (MEG) without any tasks and the subject's attention. In addition to sensory-specific areas, activation of multi-modal cortical regions responding to sensory changes is observed in functional magnetic resonance imaging (fMRI) [41] and MEG studies [42]. An automatic change-detecting system is very important because the quick detection of changes in the sensory environment is needed for survival. Thus, it seemed that a change-detecting system is a subtype of defense reactions similar to startle reflex. Recent studies on the auditory [43], visual [44], and somatosensory [34] systems have shown that acute nicotine enhances change-related cortical responses.

In a recent magnetoencephalographic study, we reported that change-related auditory N1 (Change-N1m) are inhibited when a weak prepulse precedes the test stimulus in a manner similar to PPI of startle with respect to the intensity and timing of the prepulse [45]. Since PPI of the Change-N1m is thought to reflect an inhibitory process whereby a change-driven cortical activity is protected for a certain period to complete the processing from being interfered with by subsequent events, PPI of the Change-N1m has physiological significance similar to PPI of startle. However, further studies are necessary to determine whether these two measures have common significance or mechanisms.

Therefore, in the present study, we examined the effects of acute nicotine on PPI of the Change-N1m. Since nicotine's enhancing effect has been established for PPI of startle, similar effects are expected for PPI of Change-N1m if the two share common mechanisms.

2. Materials and methods

2.1. Subjects

This experiment was performed on 12 (2 females and 10 males) healthy volunteers, aged 21–43 (32.1 ± 7.4) years. All subjects had never smoked. We instructed them to refrain from consuming alcohol and caffeine for at least 12 h prior to the experiment. All subjects had no history of mental or neurological disorders or substance abuse in the last 2 years. They received no medication at testing. All of them had a hearing threshold lower than 30 dB at 1000 Hz as assessed using an audiometer (AA-71, Rion, Tokyo, Japan). The study was approved in advance by the Ethics Committee of the National Institute for Physiological Sciences, Okazaki, Japan, and written consent was obtained from all the subjects.

2.2. Study design

Subjects attended the laboratory for two experimental sessions with the double-blind administration of a placebo or nicotine gum. The order of the sessions was randomized among subjects. For the two females, the sessions were carried out on two successive days because the menstrual cycle may affect the change-related cortical response [46,47]. For the males, the two sessions were separated by a 5- to 35-day interval. Two sessions were carried out at almost the same time in the morning. In each session, the MEG assessment was carried out twice, pre- (Pre) and post-nicotine/placebo administration (Post).

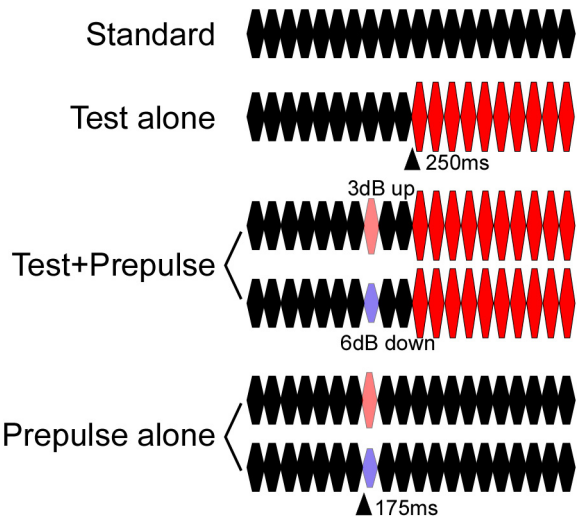

Fig. 1. Auditory stimuli. A train of brief sounds 25 ms in duration, 800 Hz in frequency, and 65 dB SPL in sound pressure was used as the standard or background stimulus. The test stimulus to evoke Change-N1m was a similar train of 10 brief sounds of 71 dB. One brief sound was inserted before the test stimulus as a prepulse.

2.3. Procedures

Experimental procedures were the same as previously reported [34]. In brief, the subjects were seated in a chair in a quiet, magnetically shielded room. At the beginning of the MEG recording, brain activity during a 2-min eye-closed rest period was recorded for assessment of the dominant alpha frequency of the background activity. Thereafter, we recorded auditory evoked magnetic fields for the baseline run (Pre). The subjects were instructed to watch a silent movie on a screen 1.5 m in front of them and to ignore sounds. They chewed the nicotine/placebo gum after the recording of the Pre run. After 30 min of chewing, 2-min background brain activity was recorded again and then the Post run was carried out. At the end of each session, we measured blood pressure and heart rate outside the MEG room.

2.4. Nicotine administration

Nicotine was administered with two mint-flavored Nicorette gums (Johnson & Johnson) containing a total of 4 mg of nicotine. In accordance with the Nicorette guidelines, subjects chewed the gum for 25 min. The 4-mg dose results in a maximum blood level of nicotine of 10–17 μg/ml after approximately 30 min, which is slightly lower than the level following smoking of a ~2 mg nicotine cigarette [48]. The placebo gum was a commercial gum similar in color, size, flavor, and texture to the nicotine gum. To reduce any sensory differences between the two gums, subjects wore a nose plug during chewing. After the chewing period, a commercial strong mint gum was chewed freely for 5 min to mask any flavor and taste differences between the nicotine and placebo gums. These procedures followed previous studies [49].

2.5. Auditory stimuli

A train of brief tone pulses was used for auditory stimuli [28,32]. The brief tone was 800 Hz in frequency, 25 ms in length (5 ms rise/fall), and 65 dB SPL in sound pressure. A clear cortical response peaking at around 130 ms is recorded by EEG (Change-N1) or MEG (Change-N1m) when any changes occur in a continuous sound [27–29,33]. An abrupt increase of sound pressure by 6 dB was used to evoke Change-N1m. As in a previous study [45], PPI was elicited by a conditioning-test paired stimulation paradigm using four types of sound stimuli (Fig. 1): 20 repeats of the same 65-dB brief tone 500 ms in total duration (Standard), 10 standard brief tones (250 ms) followed by 10 tones of 71 dB (Test alone), the Test preceded by one prepulse at 175–200 ms (Prepulse + Test), and the Standard with a prepulse (Prepulse alone). We used two prepulses, the brief sound of 68 dB (3 dB above the background) and 59 dB (6 dB below the background). Therefore, there were six sounds. The six sound stimuli were presented randomly at an even probability with a trial-trial interval of 800 ms. Sound stimuli were given binaurally through ear pieces (E-A-Rtone 3A, Aero Company, Indianapolis, IN).

2.6. MEG recordings

We recorded auditory evoked magnetic fields using a 306-channel whole-head-type MEG system (Vector-view, ELEKTA Neuromag, Helsinki, Finland) comprising