Behavioural Brain Research 256 (2013) 362–367

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short communication

Cholinesterase inhibitor, donepezil, improves visual contrast detectability in freely behaving rats

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HIGHLIGHTS

- Effect of donepezil on contrast sensitivity (CS) was tested in behaving rats.
- Rats showed low-pass spatial frequency (SF) tuning of the CS.
- The stimulus size correlated with the CS in an SF-dependent manner.
- Donepezil improved the CS in a highly sensitive SF range only.
- Acetylcholine is suggested to improve contrast detectability in a sensitive SF range.

ARTICLE INFO

Article history:
Received 21 May 2013
Received in revised form 16 July 2013
Accepted 14 August 2013
Available online 28 August 2013

Keywords:
Acetylcholine
Donepezil
Contrast sensitivity function
Spout-lever
Long-Evans rat

ABSTRACT

Acetylcholine (ACh) modulates neuronal activities in extensive brain regions to play an essential role in various brain functions including attention, learning and memory, and cognition. Although ACh is known to modulate information processing in the primary visual cortex (V1) in many species including rodent, its functional role in visual ability has remained unknown. We examined whether and how ACh influences behavioral contrast detectability in rat. The detectability was assessed as the contrast sensitivity (CS) to a grating stimulus. Measurements were performed in a two-alternative forced-choice task combined with a staircase method in freely behaving rats. The contrast sensitivity function of rats under the no drug condition showed a low-pass spatial frequency (SF) tuning peaking at 0.1 cycles/degree (cpd) of SF (SF_{peak}) that bottomed at 0.5 cpd (SF_{bottom}), which was sensitive to the stimulus size, but to neither the temporal frequency nor orientation of the stimulus. The stimulus size was correlated with the CS only at the low SF range. The effect of donepezil on the size- and SF-dependency of the CS was examined using three stimulus conditions: an easy detectability condition with large grating at SF_{peak}, a difficult detectability condition with small grating at SF_{peak}, and an upper limit SF condition with large grating at SF_{bottom}. Donepezil improved the CS at SF_{peak}, especially in the difficult detectability condition. Therefore, we conclude that ACh plays an important role in enhancing behavioral CS at sensitive SF ranges, but not in improving the upper limit of SF.

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Cholinergic neurons in the nucleus basalis of Meynert project to and affect extensive brain areas via acetylcholine (ACh), which plays an important role in various brain functions such as sensation, attention, learning and memory, and cognition [1–6]. The primary visual cortex (V1) is a major target of cholinergic projections, and its neuronal information processing is known to be modulated by ACh in many species including rodent, tree shrew, cat, and primate [5–11]. Recently, we found in rat V1 that the pharmacological activation of ACh receptors facilitates or suppresses visual responses in individual neurons and controls the gain in the relationship between the stimulus contrast (intensity of the visual input) and visual response (neuronal output) [5], an effect called response gain control. Interestingly, facilitatory modulation improved the signal-to-noise (S/N) ratio, which was assessed as the ratio of the visual response to the spontaneous discharge, and suppressive modulation enhanced the representation of the spatial phase of sinusoidal gratings, which was calculated as the F1/F0 ratio and represents the amount of temporal response modulation at the fundamental frequency (F1) of the drifting grating relative to the mean evoked response (F0) [6]. Those results suggest that ACh modulates the

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http://dx.doi.org/10.1016/j.bbr.2013.08.022

contrast sensitivity (CS) and S/N ratio of responses in the visual cortex to enhance an animal's detectability of a visual stimulus.

It has remained an open question, however, whether and how ACh improves contrast detectability in behaving rodents. Given that ACh is released in a behavioral context-dependent manner in which its release is increased during active exploration of the environment, assessing ACh effects is best when studying freely behaving animals within the bounds of normal behavior. To examine ACh effects on CS in such animals, we developed a new CS measurement system that could: (1) obtain a normal value of the CS function (CSF) from the function of the spatial frequency (SF) of the visual stimulus, (2) examine the effects of the stimulus parameters on the CSF to find the stimulus conditions that determined task difficulty, and (3) evaluate the potency of an ACh-related drug under the determined stimulus conditions.

All the experimental protocols were approved by the Research Ethics Committee of Osaka University. All the procedures were carried out in compliance with the policies and regulations of the guidelines approved by the Animal Care Committee of the Osaka University Medical School and National Institutes of Health guidelines for the care of experimental animals.

Thirteen male Long-Evans rats (200–350 g; Institute for Animal Reproduction, Ibaraki, Japan) were used. The rats were kept on a 12 h light–dark cycle, and the training and task were performed during the light period. Rats were allowed ad libitum access to water only during weekends. During the rest of the week, they obtained water by performing the required task during the training and test periods. We routinely monitored signs of possible dehydration (reduced skin tension and sunken eyes, etc.), but none were observed. To ensure adequate hydration, we weighed each animal at the beginning and end of the experiment and compared the weights to a standard weight updated weekly. The weight measured after the session was never <90% the standard weight.

The basic structure of a choice-box (Fig. 1A and B) was similar to that made by Busse et al. [12] except for the installation of a spout-lever as the operandum [13]. The front side of the box was translucent and faced an LCD monitor (mean luminance: 30 cd/m^2). The box was divided by translucent walls to produce three connected areas that each had a spout-lever in the center: a central-lever in the middle area and choice-levers in the other two. Animals could obtain the reward from a choice-lever by pulling it up, and the reward volume was changed by controlling the open time of a solenoid valve, which was manipulated by a PC. Speakers attached to the monitor gave auditory feedback signals during key states of the experiments. Animal behavior was monitored through a webcam. Software for the experimental control and stimulus presentation was written in MATLAB (Mathworks, MA, USA).

A two-alternative forced-choice (2AFC) task was combined with a staircase method [14] for direct measurement of the CS without model fitting. The rat started each trial by pulling up the central-lever, which triggered the presentation of a circular patch of sinusoidal grating to the right or left (Fig. 1B and C). The viewing distance of the stimulus center from the central-lever was 13 cm. The stimulus presentation continued until the rat pulled up either the corresponding (right/left) choice-lever. The grating location was randomly changed from trial to trial. The stimulus contrast was set initially at 100%, and the level of contrast varied from trial to trial according to the staircase method (1-up/1-down). Upon a correct choice, rats received a reward of 2–3 μL of water, and the stimulus contrast was decreased from the current level in the next trial (Fig. 1C and Supplementary Video). Upon an incorrect choice, rats received an audible sound (200–500 Hz) only, and the stimulus contrast was increased in the next trial. The stimulus contrast was decreased or increased at 1%, 4%, and 10% contrast steps in the low, middle, and high contrast range, respectively, as shown in Fig. 1D, which shows an ideal curve of the contrast change when an animal carries out the task perfectly. Each session lasted until the correct performance on the latest 10 trials fell below 60% or rats detected the 1% contrast stimulus. Fig. 1E shows actual data of a rat performance in response to a vertical grating with SF of 0.1 cycles/degree (cpd), temporal frequency (TF) of 4 Hz, and diameter of 70°. Threshold contrast ($C_{threshold}$) as a percentage was defined as the final stimulus contrast which the rat was able to choose correctly. CS was calculated by the following equation [15]: $CS = 100/C_{threshold}$.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2013.08.022.

Rats were trained in three stages for the contrast-detection task. In the first stage (1–2 d), all rats ($n = 13$) learned to obtain fluid delivered from the choice-lever automatically every 30 s or by pulling choice-lever up in a single choice-box isolated from the other areas to significantly increase the frequency of the lever manipulation (Fig. 2A; $t = 9.67$, $df = 12$, $P < 0.001$, paired t-test). In the second stage (3–6 d), the rats learned how to initiate a trial in the normal choice-box (see Fig. 1A and B). A grating was presented with a 4 kHz start-sound by pulling up the central-lever, and fluid was delivered by pulling up the correct choice-lever. When rats pulled up the incorrect choice-lever or any choice-lever before the central-lever, an audible sound was given as an instructive feedback signal. Fig. 2B shows the time from task initiation by the central-lever manipulation to choice-lever manipulation. All the rats learned this paradigm in 1 day and made rapid progress in the subsequent 2 days. In the third stage (5–10 d), rats learned that the fluid supply was associated with grating. We judged the completion of task learning when % Hit was more than 80% in 100 trials that had no change in the grating contrast. Ten of 13 rats exceeded this threshold within 12 days (Fig. 2C). The second stage overlapped with the third stage in days 5 and 6.

Using the trained rats, we measured $C_{threshold}$ at various SFs (0.05–1 cpd), with each SF being given at least 3 sessions, to obtain a CSF. Vertical grating with right/leftward drifting at a TF of 4 Hz and a diameter of 70° were used in this study. All measured rats showed low-pass tuning with a sensitivity peak (SF_{peak}) at 0.1 cpd and an upper limit SF of 1 cpd (Fig. 3A), which is in accordance with previous studies [15–17], indicating the validity of the measurement system.

To determine whether and how the grating parameters affect the CSF in advance of the donepezil experiments, we tested the influence of three parameters: TF (0–8 Hz), orientation (0–135°, 45° steps), and size (10–70°) (Fig. 3B–D). Neither TF (Fig. 3C; $F_{sf(4,365)} = 16.7$, $P < 0.001$; $F_{tf(3,365)} = 0.1$, $P = 0.954$; $F_{interaction(12,365)} = 0.7$, $P = 0.738$; two-way ANOVA) nor orientation (Fig. 3D; $F_{sf(4,588)} = 25.2$, $P < 0.001$; $F_{ori(3,588)} = 1.4$, $P = 0.136$; $F_{interaction(12,588)} = 0.5$, $P = 0.90$) had a significant influence on the CSF. On the other hand, stimulus size of the gratings significantly affected the CSF (Fig. 3B; $F_{sf(4,384)} = 11.3$, $P < 0.001$; $F_{size(3,384)} = 11.0$, $P < 0.001$; $F_{interaction(12,384)} = 2.1$, $P < 0.05$). The size-dependent difference of the CS was clearly observed at the low SF range, especially at SF_{peak} (0.1 cpd), in which the CS was positively correlated with the grating size. Thus, the grating size is a good parameter for controlling the task difficulty when the CS measurement is performed at low SF ranges, but not at high SF ranges. The high SF range is regarded as an upper limit of a rat's spatial resolution. To examine whether ACh effects depend on task difficulty and whether ACh enhances the upper limit of the spatial resolution, we tested the effects of donepezil (Eisai, Ibaraki, Japan), a cholinesterase inhibitor, on contrast detectability using three stimulus conditions: (1) an easy detectability condition defined as SF_{peak} and large size (70°), (2) a difficult detectability condition defined as SF_{peak} and small size (10°), and (3) a limit condition defined as upper limit SFs (0.5 and 1 cpd) and large size (70°).

To examine whether an increased level of ACh naturally released from cholinergic terminals, donepezil was tested in a

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