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Role of NMDA, nicotinic, and GABA receptors in the steady-state visual-evoked potential in rats ☆

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Abstract

Agonists and antagonists at the NMDA, GABA, and nicotinic acetylcholine receptors were administered to adult male rats to evaluate the contribution of these pathways to the visual-evoked potential (VEP). Rats were presented with an onset/offset pattern at a temporal frequency (4.55 Hz) resulting in a steady-state VEP. Averaged VEPs were Fourier transformed and VEP amplitudes were calculated at 1× stimulus frequency (F1) and 2× stimulus frequency (F2). About 30 min after administration, NMDA (10 mg/kg, i.p.; $n=9$) increased F1 amplitude by 350% and decreased F2 amplitude by 48%. Memantine (4.5 mg/kg, i.p.; $n=10$) increased F1 amplitude by 50%, 10 min post-injection. Similarly, nicotine (0.1 mg/kg, s.c.; $n=9$) increased F1 amplitude by 55%, 20 min after drug administration. Muscimol (1 mg/kg, i.p.; $n=10$) increased F1 amplitude significantly from 20 to 45 min post-injection. Mecamylamine (6 mg/kg, i.p.; $n=10$) decreased F2 amplitude by 70% during the 60-min testing session. Bicuculline (0–0.5 mg/kg, i.p.; $n=8-10$ rats/dose) did not significantly alter either F1 or F2 amplitudes. Results indicate important roles for glutamate and nicotinic acetylcholine receptors in both F1 and F2, while GABA receptors contribute to F1.
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1. Introduction

Visual-evoked potentials (VEPs) recorded from the visual cortex are massed neuronal responses and have been used to assess the functional integrity of visual pathways in the nervous system (Regan, 1989). Different types of VEPs may be distinguished by the visual stimuli used to elicit the VEP and have different temporal and spatial characteristics. Traditionally, researchers have often used either a flash or a pattern as a stimulus. Patterned visual stimuli have been useful to evaluate parametric features of visual pattern perception, diagnose neurological diseases, and detect neurotoxicity (Boyes, 1994). Temporally, stimulation with a sinusoidally modulated stimulus at frequencies high enough to elicit a "steady-state" response profile produces a response amenable to analysis by Fourier transform, and also enables assessment of the distinct linear and non-linear visual subsystems. The steady-state VEP, elicited by a sinusoidal on–off pattern, is comprised of a linear component that corresponds to the frequency of the stimulus presentation (F1), and a nonlinear component at double the frequency of the stimulus presentation (F2) (for a detailed review see Regan, 1989). Although steady-state pattern VEPs have numerous advantages in evaluating central nervous system function, the neurotransmitter systems involved in generating these VEPs have not been fully elucidated. Pathways that have been demonstrated to be involved in visual function include excitatory systems such

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as the glutamatergic and cholinergic signaling systems, and inhibitory GABAergic systems (Sannita, 1995).

Cholinergic, NMDA–glutamatergic and GABAergic receptors are expressed widely in the rat visual system including the retina, lateral geniculate nucleus (LGN) and visual cortex. Glutamate is the primary excitatory neurotransmitter of the afferent visual pathway between the retina and the visual cortex (Johnson and Burkhalter, 1996; Molinar-Rode and Pasik, 1992; Tamura et al., 1990). NMDA and non-NMDA receptor subunits are differentially expressed in the visual cortex (Aoki et al., 1994; Johnson et al., 1996) and NMDA–glutamate receptors in retinal ganglion cells have been shown to mediate a portion of the light-evoked response from bipolar to ganglion cells (Cohen and Miller, 1994; Chen and Diamond, 2002). Similarly, GABA is the primary inhibitory neurotransmitter in the visual system and GABA-containing neurons are abundant in the rat visual cortex (Meinecke and Peters, 1987; Rothe and Schliebs, 1989). In the retina, there are $GABA_A$ receptors on all retinal cell types and $GABA_C$ receptors in bipolar retinal cells (Feigenspan and Bormann, 1998; Djamgoz, 1995). There is also expression of all three GABA receptor types (A, B, and C) in the LGN (Zhu and Lo, 1999). Nicotinic acetylcholine receptor (nAChR) subunits have been localized in the rat LGN and retina (Clarke et al., 1985; Swanson et al., 1987; Sastry and Janson, 1994) as well as in the rat visual cortex (Aztiria et al., 2004). The global expression of NMDA–glutamatergic, GABAergic, and nicotinic receptor subunits in the visual system indicate that these systems are important for the generation of visual responses.

Agonists and antagonists to GABAergic, NMDA–glutamatergic, and nACh neurotransmitter systems have altered flash evoked and transient pattern-elicited potentials (Hetzler and Zeisset, 1997; Hetzler and Burkard, 1999; Hetzler and Theinpeng, 2004; Schwarz and Block, 1994; Kraut et al., 1990). GABAergic agonists such as diazepam decrease VEP amplitudes (Hudnell and Boyes, 1991) while direct bicuculline administration onto the visual cortex significantly altered components of a transient VEP in cats (Zemon et al., 1980). Few studies have been conducted on NMDA–glutamate receptor agonists and antagonists on VEPs and results are inconclusive as to the role of NMDA–glutamate receptors in the formation of the visual-evoked potential (Hetzler and Burkard, 1999; Schwarz and Block, 1994; Rigdon and Dyer, 1988). Nicotine administration alters components of the flash-evoked potential (FEP) in rats (Hetzler and Theinpeng, 2004) and mecamylamine, a nAChR antagonist, decreases VEP amplitude in cats (DeBruyn et al., 1991). Although these studies indicate a role of GABA, NMDA–glutamate, and nACh receptors in the visual system, the function of these neurotransmitter systems in generating steady-state visual-evoked potentials has not been examined.

However, several studies that have utilized pattern elicited VEPs to determine the effects of various compounds on the visual response. For example, steady-state pattern-evoked potentials have been used to examine visual changes associated with exposure to volatile organic compounds (VOCs; Rebert et al., 1989a,b; Boyes et al., 2003), general anesthetics (Imas et al., 2004), ethanol (Jensen and Krogh, 1984), and organophosphate insecticides (Boyes et al., 1999) among other compounds. Although these compounds were shown to produce changes in the steady-state visual-evoked potential, the mechanisms behind the changes are unknown. In vitro studies with VOCs, ethanol, and anesthetics have clearly demonstrated changes in receptor activity to these three neurotransmitter pathways (Cruz et al., 1998, 2000; Bale et al., 2002; Beckstead et al., 2000; Yu et al., 1996; Lovinger et al., 1989; Wafford et al., 1991).

The purpose of the current study was to investigate the role of the GABAergic, NMDA–glutamatergic, and nicotinic cholinergic pathways in the generation of the evoked potentials in response to a visual sine-wave grating pattern. Agonists and antagonists to these receptor systems were administered to Long-Evans rats implanted with electrodes over the visual cortex. The effects of these compounds on the VEP were measured over time in the same animal to determine the time-course of the drug. The F1 (linear) and F2 (nonlinear) responses in the VEP were determined using a Fourier transform. Exposure to VOCs such as trichloroethylene (TCE) reduced the F2 amplitude of steady-state pattern on–off VEPs (Boyes et al., 2003, 2005). In vitro, TCE or other VOCs with similar actions have been shown to be NMDA antagonists, nAChR antagonists and $GABA_A$ agonists. Therefore, we hypothesized that treatment with drugs shown to be NMDA antagonists, nAChR antagonists or $GABA_A$ agonists would also reduce F2 amplitude. In addition, we hypothesized that drugs with the opposite pharmacological actions would increase F2 amplitude.

2. Methods

2.1. Animals

80-day-old male Long-Evans rats (350–450 g, $n=189$ rats) were obtained from Charles River Laboratories (Raleigh, NC). Rats were housed individually in polycarbonate cages and provided ad libitum access to tap water and rat chow (PMI #5001, LabDiet). Animals were allowed to acclimate for a least 1 week prior to surgery. The animal colony had an ambient temperature and relative humidity of 22 ± 2 °C and $50\pm10\%$, respectively. Rats were on a 12:12 h light/dark cycle where lights were on from 6:00 am to 6:00 pm. All aspects of the care and treatment of laboratory animals were approved by the Institutional Animal Care and Use Committee and were in compliance with applicable federal guidelines for laboratory animal experimentation.

2.2. Electrode implantation

Electrodes constructed from Nichrome wires soldered to stainless steel screws ($00-90\times1/16$) were implanted into the rat skull, epidurally, as previously described (Boyes et al., 2003). Briefly, rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and recording electrodes were implanted in the following locations: 1 mm anterior to lambda and 4 mm left of the midline overlying the primary visual cortex, and 2 mm anterior to bregma and 2 mm left and right to the midline for the ground and reference electrodes, respectively. After

implantation, the electrodes were connected to a nine-pin connector (WirePro model 223-1609; Resource Electronics, Raleigh, NC), the entire assembly was encased in acrylic, and the wound was sutured. Approximately 1 week was allowed for recovery before VEP testing.

2.3. Visual stimuli

The visual stimulus pattern was a vertical grating with a mean sinusoidal spatial luminance profile of 10 cd/m^3, spatial frequency of 0.16 cpd, visual contrast of 60%, and was temporally modulated in an on–off fashion with a 4.55 Hz sinusoid. A value of 0.16 cpd was selected because it is approximately at the peak of the contrast sensitivity function of the pigmented rat. A value of 60% was selected because it fell well within the linear portion of the video monitor luminance response function and yielded a strong evoked potential. Visual stimuli were presented on a monitor (ViewSonic 15, model 1564 M; Walnut, CA) located approximately 15 cm from the rat's eyes and were generated from a computer-based system described in detail in Hamm et al. (2000). Briefly, stimulus patterns were provided to the memory of a super-VGA graphics display card. The "green" video card output signal was then processed with analog circuitry and analog multipliers were used to set the contrast, apply the temporal modulation, and set the overall luminance. Sixteen-bit D/A converters were used to generate the percent contrast and luminance control signals.

2.4. VEP testing

For testing, rats (85–99 days) remained awake and were restrained using a plastic cone (Braintree Scientific, Braintree, MA) with portions removed to uncover the rat's eyes, nose, and ears. The rats were placed in a darkened Faraday cage 15 cm from the pattern generating monitor and the electrode headset was connected to a cable exiting the Faraday cage chamber to the amplifier. After 5–10 min for acclimation, rats were presented with the previously described on–off pattern. Visual-evoked potentials were measured in 5 second epochs, amplified and band-pass filtered (1–100 Hz). A total of 25 epochs were averaged for each time point. After obtaining baseline VEP measurements, rats were injected with vehicle or one of the test compounds and VEP measurements were collected at 10, 20, 30, 45, and 60 min post-injection. Averaged evoked potentials were then submitted for spectral analysis using a computer-based system described in detail in Hamm et al. (2000). The spectral amplitude at the stimulus rate (F1) and twice the stimulus rate (F2) were recorded as dependent variables.

2.5. Test compounds

All administered drugs were purchased from Sigma-Aldrich (St. Louis, MO). The drugs evaluated were *N*-methyl-D-aspartate (NMDA), memantine hydrochloride, nicotine hydrogen tartrate, mecamylamine hydrochloride, muscimol, and bicuculline (Table 1). With the exception of NMDA and bicuculline, the drugs were dissolved in saline. NMDA was dissolved with an equimolar concentration of NaOH in saline, and bicuculline was dissolved in saline/10% DMSO. Doses of drug administered were as follows: NMDA (i.p.)—1, 5, 10 mg/kg; memantine (i.p.)—4.5, 10, 15 mg/kg; nicotine (s.c.)—0.1, 0.5 mg/kg; mecamylamine (i.p.)—3, 6 mg/kg; muscimol (i.p.)—1 mg/kg; bicuculline (i.p.)—0.1, 0.2, 0.25, 0.3, 0.5 mg/kg. Dose ranges, routes, and preparations for each compound were determined from selected studies (NMDA, Willmore et al., 2001a,b; memantine, Zajaczkowski et al., 1996; Willmore et al., 2001a,b; nicotine, Hetzler and Theinpeng, 2004; Levin and Simon, 1998; mecamylamine, Bushnell et al., 1997; Decker and Majchrzak, 1992; muscimol, Oksztel et al., 2002; Zarrindast et al., 2001; Bizot et al., 1999; bicuculline, Zarrindast et al., 2001). Pilot studies were conducted to determine appropriate drug doses below those that produce adverse effects such as seizures and/or drowsiness and determine the optimal time-course for the ensuing studies. With two drugs, bicuculline (1 mg/kg, i.p., $n=3$) and NMDA (30 mg/kg, i.p., $n=3$) animals displayed adverse seizurogenic signs including increased salivation and urination as well as inability to measure steady-state VEPs (data not shown). A control group of rats was administered saline to determine if the measured F1 or F2 components changes over the 60-min time period.

2.6. Statistical analysis of VEP measurements

A mixed-model repeated-measures two-way ANOVA was utilized to determine the significance of drug effects and time. The time measurements were made within the same animal, but the treatment groups were comprised of different animals, so a mixed model approach was necessary. The ANOVA was conducted using the Proc GLM protocol (SAS, Cary, NC) with time as the repeated measure and treatment as a between subjects variable. If the ANOVA was significant, then

Table 1
Summary of selected receptor agonists and antagonists on F1 and F2 amplitude

Receptor	Compound	F1		F2	
		Significant effect	Dose-related	Significant effect	Dose-related
NMDA–glutamate	NMDA (agonist)	↑	↑	↓	↓
	Memantine (antagonist)	↑	–	No change	–
AChR	Nicotine (agonist)	↑	–	No change	–
	Mecamylamine (antagonist)	No change	–	↓	↓
GABA	Muscimol (agonist)	↑	–	No change	–
	Bicuculline (antagonist)	No change	–	No change	–

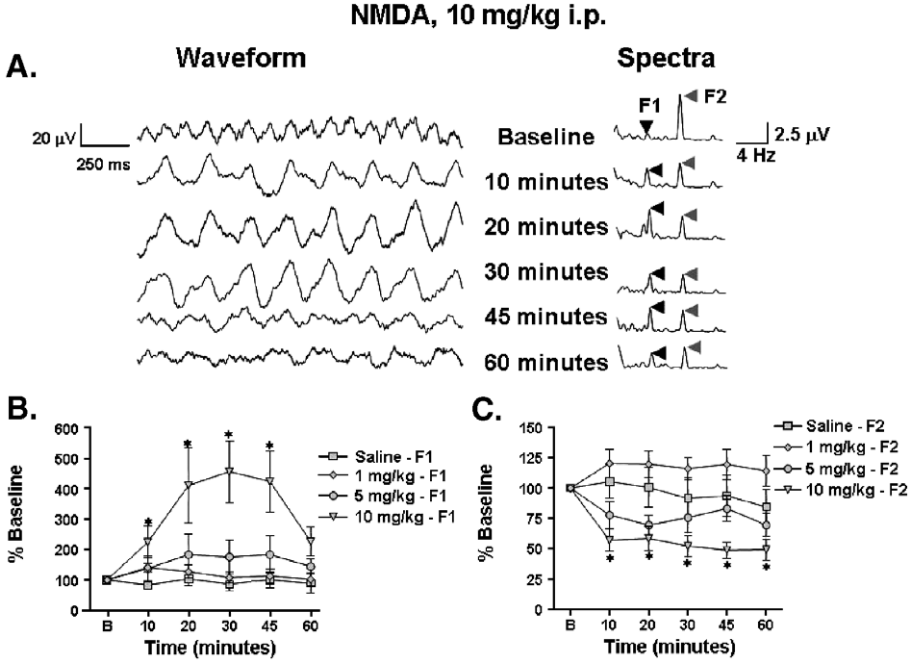

Fig. 1. NMDA (10 mg/kg) significantly increases F1 and decreases F2 amplitude. (A) Representative VEP waveforms from one rat dosed with 10 mg/kg NMDA are depicted in the left panel. On the right panel are the averaged spectral transforms of the VEP waveforms over 60 min ($n=8$). F1 and F2 peaks are indicated on the figure by the respective arrows and correspond to the amplitude at 1× frequency rate, 4.5 Hz (F1) and the measured amplitude at 2× frequency rate, 9.0 Hz (F2). (B) F1 amplitudes of animals dosed with NMDA (0–10 mg/kg, $n=8$–10 animals/dose) are plotted as a function of percent change from the baseline F1 amplitude over time. (C) F2 amplitudes are plotted as a function of percent change from the baseline F2 amplitude over time. *Effect was significant with respect to the saline (0 mg/kg) group ($p<0.05$, mixed repeated measures two-way ANOVA, Tukey's post-hoc test).

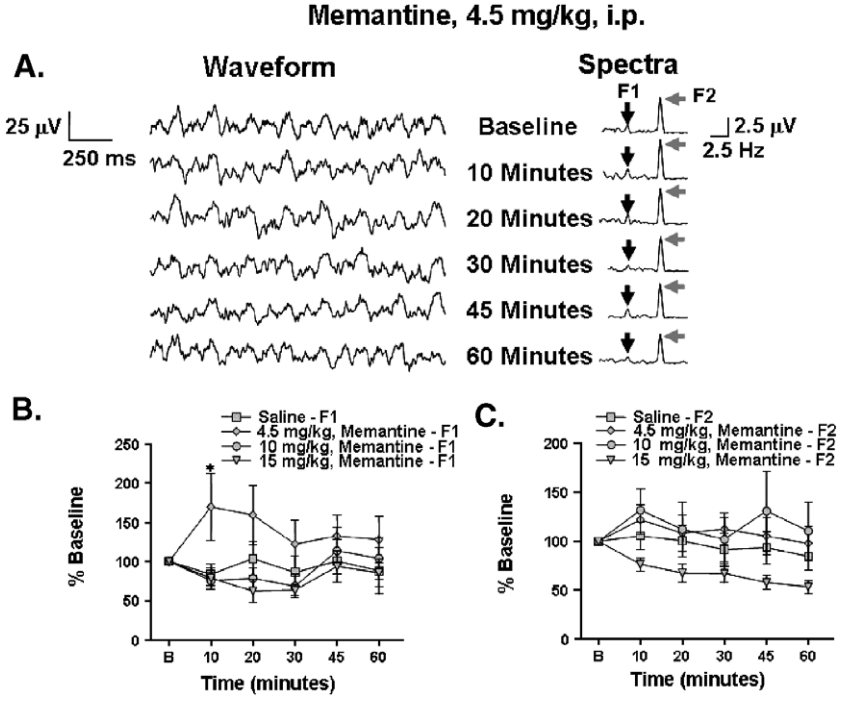

Fig. 2. Memantine increases F1 amplitude at a 4.5 mg/kg dose. (A) Representative VEP waveforms from one rat dosed with 4.5 mg/kg memantine are depicted in the left panel. On the right panel are the averaged spectral transforms of the VEP waveforms from all the rats dosed with 4.5 mg/kg memantine ($n=9$). F1 and F2 peaks are indicated on the figure by the respective arrows and correspond to the amplitude at 1× frequency rate, 4.5 Hz (F1) and the measured amplitude at 2× frequency rate, 9.0 Hz (F2). (B) F1 amplitudes of animals dosed with memantine (0–15 mg/kg, $n=8$–10 animals/dose) are plotted as a function of percent change from the baseline F1 amplitude over time. (C) F2 amplitudes are plotted as a function of percent change from the baseline F2 amplitude over time. *Effect was significant with respect to the saline (0 mg/kg) group ($p<0.05$, mixed repeated measures two-way ANOVA, Tukey's post-hoc test).

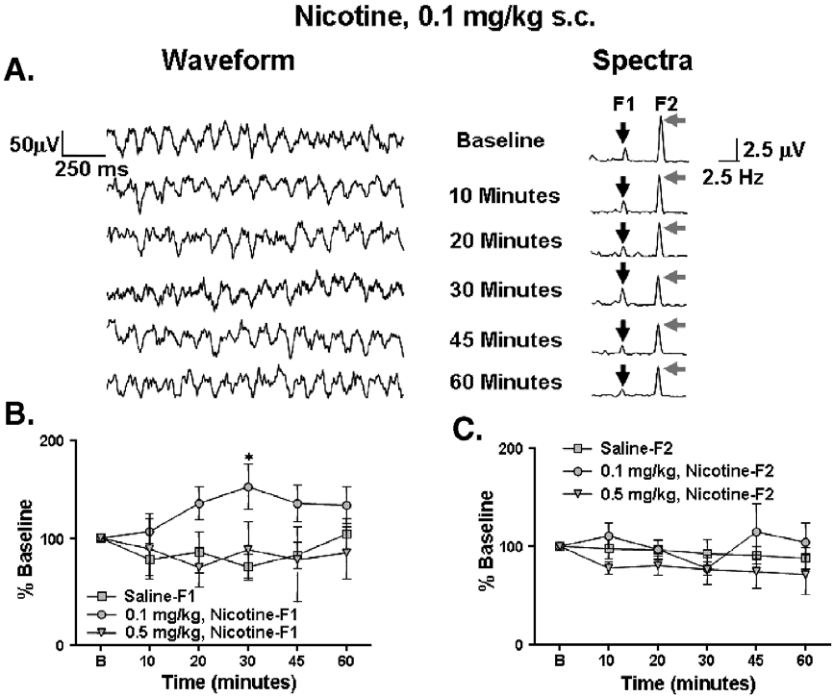

Fig. 3. Nicotine (0.1 mg/kg, s.c.) increases F1 amplitude. (A) Representative VEP waveforms over a 60-min testing session from a rat dosed with 0.1 mg/kg nicotine. The VEP waveforms from each dosed animal ($n=10$) were transformed using Fourier analysis and the spectra are displayed in the right panel. (B) F1 amplitudes of animals dosed with nicotine (0–0.5 mg/kg, $n=8–10$ animals per dose) plotted as a function of percent change from the baseline F1 amplitude over the 60-min testing session. (C) F2 amplitudes are plotted as a function of percent change from the baseline F2 amplitude. *Effect was significant with respect to the saline (0 mg/kg) group ($p<0.05$, mixed repeated measures two-way ANOVA, Tukey's post-hoc test).

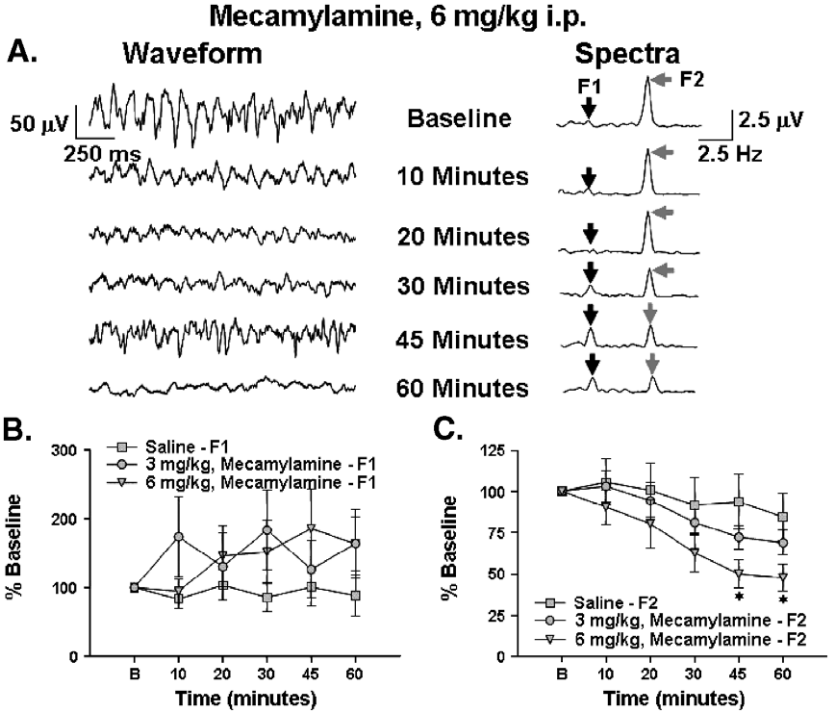

Fig. 4. Mecamylamine (6 mg/kg, i.p.) significantly decreases the F2 VEP response. (A) Representative VEP waveforms from one rat dosed with 6 mg/kg mecamylamine over a 60-min testing session are depicted in the left panel. The VEP waveforms from each dosed animal ($n=10$) were transformed using Fourier analysis and the spectral transforms are shown in the right panel. F1 and F2 peaks are indicated on the figure by the respective arrows and correspond to the amplitude of the potential at the stimulus frequency (F1, 4.5 Hz) and the amplitude of the potential at double the stimulus frequency (F2, 9.0 Hz). (B) F1 amplitudes of rats dosed with mecamylamine (0–6 mg/kg, $n=8–10$ animals per dose) are plotted as a function of percent change from the baseline F1 amplitude. (C) F2 amplitudes are plotted as a function of percent change from the baseline F2 amplitude. *Effect was significant with respect to the saline (0 mg/kg) group ($p<0.05$, mixed repeated measures two-way ANOVA, Tukey's post-hoc test).

treatment groups were compared using Tukey's post-hoc test ($p<0.05$).

3. Results

All rats remained awake and kept their eyes open throughout the testing session. Saline administered i.p. or s.c. to the rats did not significantly change the F1 or F2 amplitude with respect to the baseline measurement (Figs. 1–6, saline groups). The baseline VEP measurements indicated that the rats typically had a strong F2 response in comparison to the F1 response. A summary of all the effects of the drugs tested is presented in Table 1.

3.1. NMDA–glutamatergic system

NMDA and memantine were administered to evaluate the contribution of both activation and inhibition, respectively, of NMDA receptors to steady-state VEPs. NMDA effects on the steady-state VEP were dose-dependent as F1 amplitude increased and F2 amplitude decreased (Fig. 1A), reaching significance at 10 mg/kg. Ten min after NMDA (10 mg/kg, i.p) administration, there was a visible change in the VEP waveform that was also reflected in the spectra (Fig. 1A). Between 10 and 60 min after injection of 10 mg/kg NMDA, the F1 peak was significantly increased from baseline (Fig. 1B; $n=9$, $F(3,33)>1.45$, $p<0.05$, Tukey's post-hoc test). About 60 min after injection F1 amplitude had returned to control levels. The amplitude of F2 was significantly reduced by NMDA (10 mg/kg) from 10 min to 60 min after treatment in comparison to the saline-treated group (Fig. 1C; $F(3,33)>0.34$, $p<0.05$, Tukey's post-hoc test). The F2 amplitude had not returned to control levels by 60 min after treatment, the last time point evaluated.

The lowest dose of memantine administered (4.5 mg/kg) significantly increased F1 amplitude (Fig. 2). Representative VEP waveforms showed changes over the 60-min time period that were reflected in the spectra (Fig. 2A). F1 amplitudes were increased by 50% at the 10-min time-point with the 4.5 mg/kg memantine dose (Fig. 2B; $F(3,33)=4.47$, $p<0.05$, Tukey's post-hoc). Although there were increases in F1 amplitude with this dose, the increases were not as high as with the NMDA administration. Conversely, the two higher memantine doses (10 and 15 mg/kg) did not significantly alter F1 amplitude from saline-treated animals. Similarly, memantine (4.5–15 mg/kg, i.p.) did not have a significant effect on F2 amplitude (Fig. 2C), although the highest dose group (15 mg/kg) had lower mean F2 amplitudes than the other groups.

3.2. Nicotinic–cholinergic system

Previous studies have demonstrated the involvement of the nicotinic cholinergic system in other types of visual-evoked potentials (Hetzler and Theinpeng, 2004; Woodson et al., 1982). In order to demonstrate involvement of nicotinic cholinergic activity in the steady-state VEP, nicotine, an

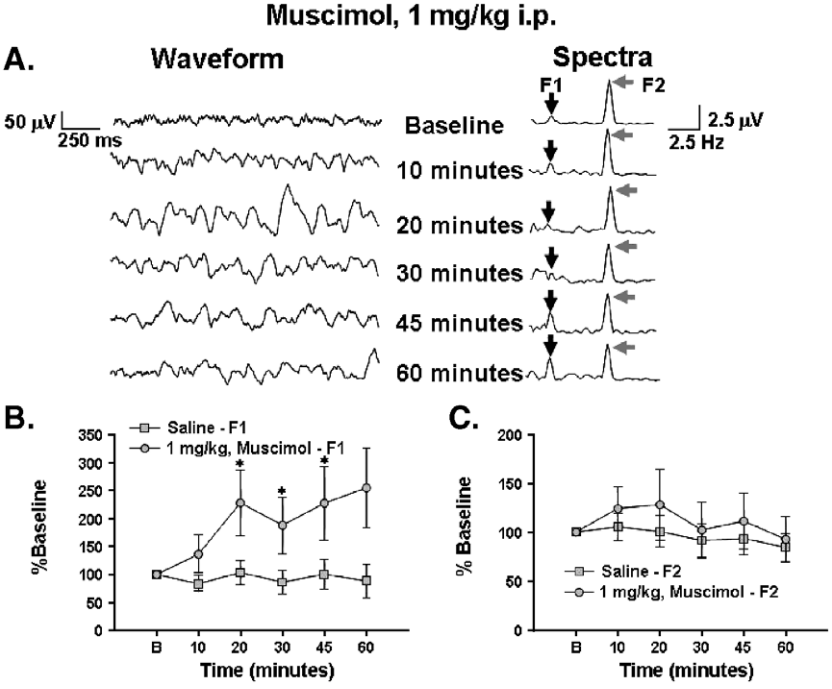

Fig. 5. Muscimol (1 mg/kg, i.p.) significantly increases F1 amplitude. (A) Representative waveforms from one rat dosed with 1.0 mg/kg muscimol are depicted in the left panel over the 60-min testing session. The waveforms were transformed using a Fourier transform and the averaged spectral transforms ($n=10$) are displayed in the right panel. F1 and F2 peaks are indicated on the figure by the respective arrows and correspond to the amplitude of the potential at the stimulus frequency (F1, 4.5 Hz) and the amplitude of the potential at double the stimulus frequency (F2, 9.0 Hz). (B) F1 amplitudes of animals dosed with muscimol (0 and 1 mg/kg, $n=9$–10 animals per dose) are plotted as a percentage of the baseline F1 amplitude over time. (C) F2 amplitudes are plotted as a function of percent change from the baseline F2 amplitude over time. *Effect was significant with respect to the saline (0 mg/kg) group ($p<0.05$, mixed repeated measures two-way ANOVA, Tukey's post-hoc test).

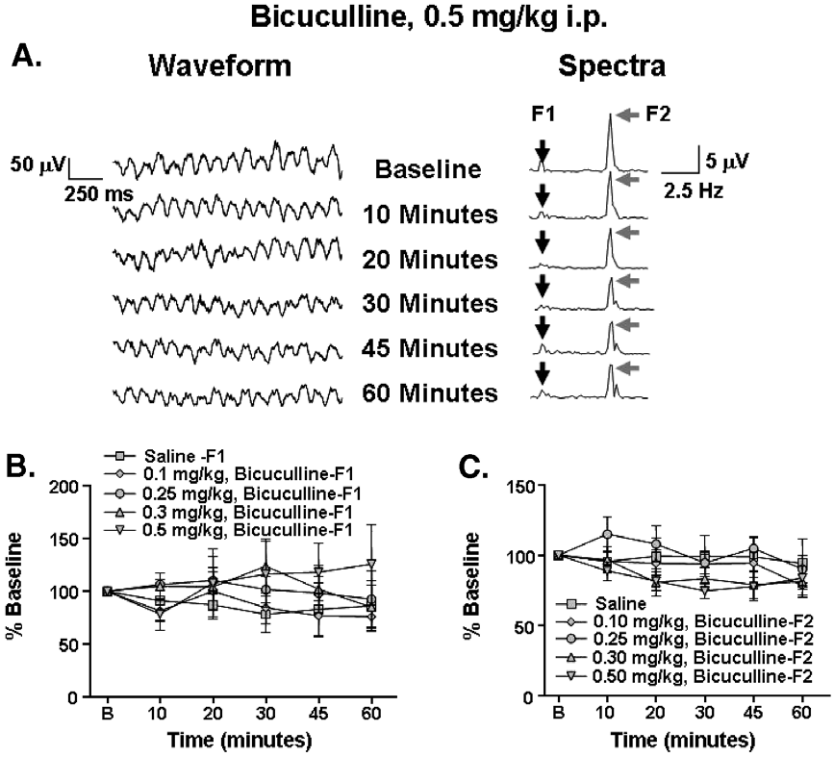

Fig. 6. Bicuculline does not alter F1 or F2 VEP amplitudes. (A) Representative VEP waveforms measured from baseline to 60 min from one rat dosed with 0.5 mg/kg bicuculline. The waveforms were transformed using a Fourier transform and the averaged spectral transforms ($n=10$) are displayed in the right panel. F1 and F2 peaks are indicated on the figure by the respective arrows and correspond to the amplitude of the potential at the stimulus frequency (F1, 4.5 Hz) and the amplitude of the potential at double the stimulus frequency (F2, 9.0 Hz). (B) F1 amplitudes of animals dosed with bicuculline (0–0.5 mg/kg, $n=8–10$ animals per dose) plotted as a function of percent change from the baseline F1 amplitude over time. (C) F2 amplitudes are plotted as a function of percent change from the baseline F2 amplitude.

agonist to the nicotinic acetylcholine receptor, and mecamylamine, an antagonist, were adminitered to rats. Nicotine (0.1 mg/kg, s.c.) significantly increased F1 amplitudes (Fig. 3A) without altering F2 amplitudes (Fig. 3B). Changes in VEPs from rats dosed with 0.1 mg/kg nicotine were observed 20–40 min after administration ($F(2,24)>0.28$, $p<0.05$, Tukey's post hoc). This effect was transient because the VEP returned to pre-dosed conditions 60 min after nicotine administration (Fig. 3C; $F(2,24)=1.35$, $p=0.27$). A higher dose, 0.5 mg/kg, did not produce any significant changes in F1 or F2 amplitudes during the 60-min testing session.

In contrast to nicotine, the nAChR antagonist, mecamylamine, significantly decreased F2 amplitude over time without changing F1 amplitude. VEPs measured from rats dosed with 6 mg/kg mecamylamine (i.p.) changed significantly, which is reflected in the spectra as the decrease in the F2 peak over the 60-min testing session (Fig. 4A). Conversely, F1 amplitudes in the mecamylamine groups (3 and 6 mg/kg) were not significantly different from the saline groups (Fig. 4B). Mecamylamine (6 mg/kg) decreased F2 amplitude by 50% at 45 to 60 min with respect to the saline group (Fig. 4C; $F(2,26)=0.96$, 45 min; 1.08, 60 min, $p<0.05$, Tukey's post hoc).

3.3. GABAergic system

Due to the high expression of GABA receptor subunits throughout the rat visual system (Meinecke and Peters, 1987; Sannita, 1995) as well as known contributions of the GABAergic system to the flash-evoked potential (Zemon et al., 1980; Hudnell and Boyes, 1991; Hetzler and Zeisset, 1997), muscimol and bicuculline were administered to assess the contribution of the GABAergic system to the generation of the steady-state VEP. Muscimol, a GABA receptor agonist, was administered to rats to determine the involvement of GABAergic systems. About 20 min after dosing with muscimol (1 mg/kg, i.p.), the VEP waveform was altered with respect to baseline (Fig. 5A). VEP changes were sustained through the 45-min time-point. F1 amplitude was significantly increased in comparison to the saline group from 20 to 45 min (Fig. 5B; $F(1,17)>1.97$, $p<0.05$, Tukey's post hoc). There were no significant changes in F2 amplitude with this dose of muscimol during the 60-min testing session (Fig. 5C; $F(1,17)>0.87$, $p>0.05$).

Bicuculline, a $GABA_A$ receptor antagonist, was administered to the rats to determine if blockade of GABA receptors would alter VEP amplitude. Although animals injected with 0.5 mg/kg bicuculline did not display a change in the F2 amplitude, when a group average spectra was tabulated, there were changes in the F2 peak that corresponded to a frequency shift which resulted from VEP waveform phase differences between the rats (Fig. 6A). None of the administered doses (0.1–0.5 mg/kg) produced a significant change from the saline group in F1 (Fig. 6B) or F2 amplitudes (Fig. 6C).

4. Discussion

The results of this study illustrate a differential involvement of three neurotransmitter signaling systems, NMDA–glutamate, GABA, and nACh, in pattern elicited VEP responses (see Table 1). This study demonstrated that NMDA (NMDA–glutamate receptor agonist) increased the F1 amplitude of the VEP and decreased the F2 amplitude in a dose and time-dependent manner. Similarly, memantine, an NMDA–glutamate receptor antagonist, also increased the F1 amplitude, but did not alter the F2 amplitude at the lowest dose administered (4.5 mg/kg). Nicotine (0.1 mg/kg) increased F1 amplitude and the nAChR antagonist, mecamylamine (6 mg/kg), decreased F2 amplitude. Finally, the GABA receptor agonist, muscimol, increased F1 amplitude in a time-dependent manner without changing F2 and bicuculline, the $GABA_A$ receptor antagonist, did not change F1 or F2 components significantly.

Pattern-elicited steady-state VEPs, like FEPs and transient VEPs, are generated by the visual cortex (Herr and Boyes, 1995). Although there are similarities of effects of the many drug classes with pattern VEPs and FEPs, some drugs may alter the two responses very differently (Boyes and Dyer, 1984). It should also be noted that the maximally stimulated areas in the visual cortex are different between pattern- and flash-evoked responses (Dyer et al., 1987). Specifically, major components of pattern VEPs are predominantly elicited over area 17 in the rat visual cortex whereas some components of the FEPs can be recorded outside of this area (Onofrj et al., 1985). In addition, the transition (with increasing temporal frequency) from transient responses, with reliably identifiable peaks, to steady-state responses, with sinusoidal continuous responses, causes the relationship between individual transient peak waveforms and steady-state response frequency components to become unclear (Boyes and Dyer, 1983). Therefore, the results from the FEP studies can not be directly compared to the results from the present study although it does provide information as to the involvement of the neurotransmitter systems in the elicitation of a visual-evoked response. However, the FEP and transient pattern VEP studies are useful in validating some of the results that were obtained in the present study.

The NMDA and memantine findings indicate that the NMDA–glutamate receptor system is important for the generation of the F1 component of the steady-state VEP. The observations with the NMDA drug administration are in contrast to results from previous studies with NMDA receptor agonists and antagonists. In another study, NMDA (4 nmol ~0.6 mg/kg) was applied directly to the visual cortex in pentobarbital-anesthetized rats and did not produce any significant changes in the visual-evoked potential alone (Schwarz and Block, 1994). These results are similar to the absence of effects with 1 and 5 mg/kg NMDA doses, but different from the significant effects observed with the 10 mg/kg NMDA dose. The contrast in findings may be partially related to the differences in the administration route between the two studies. A systemic (i.p.) administration of NMDA would also have effects on other parts of the visual system (retina, LGN) as well as other compartments in the brain, whereas the local application of NMDA would be expected to affect primarily the visual cortex.

The F2 amplitude decrease with 10 mg/kg NMDA was similar to effects with GABAergic compounds such as diazepam (Hudnell and Boyes, 1991). NMDA administration also increased F1 which may correlate to the F2 amplitude decrease in this instance. In a previous study, exposure to toluene, a volatile organic compound that inhibits NMDA receptor function in vitro (Cruz et al., 1998), significantly decreased F2 amplitude in rats (Boyes et al., 2000). However, toluene does modulate the function of several other receptors in addition to the NMDA receptor and those receptors may contribute to the decrease in F2 amplitude.

It is possible that the NMDA effect on F2 amplitude may have been an indirect result of activation of GABA inhibitory signals. In the rat visual cortex, increased activation of cortical cells in area 17 (layer IV, visual cortex) results in an increase in $GABA_B$-mediated IPSCs (Shao and Burkhalter, 1999). Thus, excess administration of NMDA (10 mg/kg) could potentially produce increased GABA signaling leading to an overall inhibition in VEP response. Another possibility may be based on the localization of NMDA receptors in the rat visual cortex. These receptor types are primarily located in layer II of the primary visual cortex in adult rats (Johnson et al., 1996). Thus, the NMDA–glutamatergic neurons may synapse onto inhibitory GABAergic neurons in lower layers. An increased excitation of GABAergic neurons would result in a response emulating a GABAergic compound such as diazepam (i.e. decreased F2 amplitude; Hudnell and Boyes, 1991). However, when muscimol (1 mg/kg), another GABAergic compound, was administered in the present investigation, F2 amplitude was not affected at this dose level.

Memantine, an NMDA receptor antagonist, significantly increased F1 amplitude at a low dose (4.5 mg/kg), whereas higher doses did not produce any effect on the VEP waveform. Previous studies with other NMDA–receptor antagonists have also demonstrated effects on other types of visual-evoked potentials. For example, ketamine significantly increased P1 amplitudes and decreased N1, P3, and N3 amplitudes of flash-evoked potentials obtained from rats (Rigdon and Dyer, 1988). MK-801 (dizocilpine) also altered flash-evoked potentials in rats by increasing N1 and P3, without changing P1 and N3 (Hetzler and Burkard, 1999). Administration of AP7 into the dorsal lateral geniculate nucleus decreased the amplitude of N1 and P1 in transient visual-evoked potentials from anesthetized rats (Schwarz and Block, 1994). Although all compounds produced effects, all three studies collectively had conflicting results, depicting the complexity underlying visual system responses. It is interesting that a low dose of memantine and a high dose of NMDA both significantly increase F1 amplitude, although more studies need to be conducted in order to understand why the NMDA receptor agonist and antagonist produced a similar alteration in the steady-state VEP. One possibility is that the linear F1 response is the default or natural state of the system response and nonlinear F2 responses may be added on top of

F1 via NMDA receptor-mediated activity. As a result, blocking the NMDA receptor could cause the system to lose F2 and revert to F1. High doses of NMDA might also do this via a prolonged depolarization block and low doses of memantine also demonstrate this process.

Nicotine significantly increased F1 amplitude at a low dose, without producing an effect at a higher dose. The F1 changes were subtler in comparison to the NMDA treatment. This finding correlates to other VEP studies using nicotine. For example, nicotine (0.4–1.0 mg/kg) significantly altered the visual cortex FEP in rats by increasing and decreasing the amplitude of the specific FEP components (Hetzler and Theinpeng, 2004). When nicotine-only cigarettes (1.34 mg) were administered to humans, there were increases in the measured peak-to-peak amplitudes from the visual-evoked response within 6 min of smoking the cigarette (Woodson et al., 1982). Conversely, mecamylamine decreased the F2 amplitude of the steady-state VEP in a dose- and time-dependent manner. Other studies with mecamylamine on visual-evoked potentials have yielded comparable results. Our current finding is in agreement with DeBruyn et al (1991) who reported that pretreating cats with mecamylamine decreased transient VEP amplitude by 30%. Furthermore, Parkinson et al (1988) found that mecamylamine significantly decreased the number of evoked responses in the cat visual cortex. In this same study, nicotinic ACh binding sites were isolated in layer IV of the visual cortex. Thus, nAChRs are implicated in visual signaling since layer IV is where the LGN input terminates.

In the LGN, presynaptic nAChRs enhance both glutamate and GABA release. Specifically, in the chick ventral LGN, application of carbachol, an AChR agonist, resulted in a significant increase in bicuculline-sensitive spontaneous post-synaptic currents (McMahon et al., 1994) indicating that the postsynaptic currents in the LGN are mediated by $GABA_A$ receptors. A subsequent study examined further the role of pre-synaptic nAChRs in the LGN (Guo et al., 1998). Application of nAChR antagonists, dihydro-β-erythroidine and α-bungaro-toxin on LGN slices blocked glutamatergic postsynaptic currents indicating that some nAChRs also promote glutamate release. Thus, activation of nAChRs in the LGN resulted in glutamate and GABA release. Direct activation of nAChRs in the visual cortex in layer IV where the majority of these receptors are expressed could also account for the effects observed with nicotine and mecamylamine. The summation of effects from the three collective targets may account for the marginal effects observed with nicotine on the steady-state VEP possibly by producing counteracting effects in different areas of the visual system.

With respect to mecamylamine and nicotine, inverse effects on the steady-state VEP may not be possible. Finding a significant decrease in F1 amplitude is unlikely in saline-treated animals because the F1 amplitude is generally below 1 μV in comparison to an average of 5 μV for the F2 amplitude. As for the F2 amplitude, significant increases in this component may not be possible if the response were already maximal. However, the stimulus contrast was only 60% which does not elicit a maximal response in rats (Boyes, 1994). Increased amplitudes of transient pattern-evoked potentials have been observed in rats treated with the insecticides chlordimeform and amitraz as well as the drug clonidine (Boyes and Dyer, 1984; Boyes and Moser, 1987; Boyes and Moser, 1988), which are thought to act as α_2-adrenergic receptor agonists. However, those compounds have not been tested on steady-state pattern visual potentials.

The GABAergic agonist, muscimol significantly increased F1 amplitude over time. Thus, there is evidence of GABAergic modulation in the formation of a VEP which is consistent with other previous studies. Other studies have demonstrated that GABAergic agonists significantly alter visual-evoked potential waveforms. THIP, a GABA receptor agonist, produced significant changes in the flash-evoked potential components, particularly a decrease in N1 and an increase in P2, when administered to rats (Hetzler and Zeisset, 1997). Interestingly, THIP significantly reduced N1 amplitude in the transient-evoked potential which was opposite to the bicuculline effects in cats (Zemon et al., 1980). However, the significant F1 amplitude increase with muscimol administration is in contrast to a previous study of rats exposed to diazepam, another $GABA_A$ receptor modulator. When diazepam was administered, there was a significant decrease in F2 amplitude without changing F1 (Hudnell and Boyes, 1991). The discrepancies in the results can be partially attributed to diazepam, a benzodiazepine, binding to only the $GABA_A$ receptor, whereas muscimol can also activate $GABA_B$ and $GABA_C$ receptor types.

Modulation in visual function with GABAergic compounds is not surprising considering the abundance of GABA terminals in the rat visual cortex. GABA terminals are found in every layer, with the greatest density of synaptic contacts occurring in layer IV. Furthermore, using immunolabeling techniques, GABAergic neurons were found uniformly in layer II through VI, and there was significantly more neuronal staining in layer I (Meinecke and Peters, 1987).

Muscimol significantly increased only the F1 amplitude in the present study and diazepam significantly decreased F2 amplitude; therefore, bicuculline should have theoretically decreased the F1 or increased the F2 amplitude. However, bicuculline (0–0.5 mg/kg, i.p.) did not significantly alter the steady-state visual-evoked potential. As mentioned earlier, F1 amplitude is normally small and it is difficult to observe a decreased F1. Therefore, even if bicuculline were decreasing the F1 amplitude, the effect may not be detectable. Since bicuculline specifically inhibits $GABA_A$ receptors, it was expected that the F2 amplitude would significantly increase. Interestingly, bicuculline did not have any effect on the pattern-elicited VEP at any of the doses tested in this study. One possible explanation for the lack of effects may be that the bicuculline dose was insufficient. Higher doses were not administered due to seizurogenic effects and the resultant non-specific effects on the VEP. Bicuculline doses as low as 2.5 mg/kg (s.c.) produce rhythmic EEG episodes (Matejovska et al., 1998) in rats. The rhythmic EEG episodes are characteristic of an initial seizure response in animals and humans. At the highest dose of bicuculline administered

(0.5 mg/kg, i.p.), animals were salivating uncontrollably and there was increased urination by the end of the test session in comparison to saline-dosed animals (personal observations). The results presented in this study are in contrast to an earlier finding with bicuculline effects on evoked potentials. Anesthetized cats (Zemon et al., 1980) were continuously perfused with bicuculline (5 mM ~ 1.8 mg/ml) on the visual cortex and the initial negative wave (N1) amplitude significantly increased and the second positive wave amplitude (P2) significantly decreased in transient visual-evoked potentials. However, the generated VEP was not a steady-state waveform and the cats were anesthetized.

Previous results have demonstrated that exposure to TCE, a VOC, reduces the F2 amplitude in Long-Evans rats (Boyes et al., 2003, 2005). In vitro, TCE and other VOCs inhibit NMDA receptors (Cruz et al., 1998, 2000), potentiate $GABA_A$ receptors (Beckstead et al., 2000) and inhibit nAChRs (Bale et al., 2002, 2005). Therefore, based on these effects, it was hypothesized that similar to TCE, memantine, mecamylamine, and muscimol would decrease F2 amplitude and NMDA, nicotine, and bicuculline would increase F2 amplitude. Mecamylamine was the only drug that decreased F2 amplitude out of the drugs that were hypothesized to decrease F2 amplitude (memantine and muscimol). Interestingly, none of the drugs increased F2 amplitude. Therefore, the resulting effects of TCE and other neurotoxicants on F2 amplitude may not only encompass these three receptor systems but also other receptor systems that have not been yet shown to be sensitive to these VOCs. Furthermore, the effect may be due to a combination of several neurotransmission modifications in the visual system. As a result, these findings illustrate the complexity in the formation of the steady-state VEP.

Overall, the results from the present study demonstrate the involvement of the NMDA–glutamatergic, nicotinic acetylcholinergic, and GABAergic systems in the generation of a steady-state visual-evoked potential. More discrete studies will need to be performed, both in vivo and in vitro, to fully elucidate the individual and collective role of neurotransmission during a visual response. It should be noted that the systemic administration of specific receptor agonists and antagonists may affect visual targets in the retina, LGN, and the visual cortex. Therefore, more information on these selective areas of the visual system is necessary in order to accurately confirm the role of each neurotransmitter and their receptors in various portions of the visual system. Knowledge of the contribution of various neurotransmitter systems to physiological responses such as VEPs will further elucidate molecular targets that are affected by genetic disorders and/or environmental agents.

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