The modulation of Group I metabotropic glutamate receptor on synaptic transmission efficiency in the Primary Visual Cortex of Monocular Deprivation Amblyopia Rat

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Abstract

Background :The occurrence of amblyopia is closely related to the glutamate receptors in visual cortex. The expression of metabotropic glutamate receptor 1 (mGluR1) in the visual cortex of rats with amblyopia has been proved to decrease, however, the role of mGluR1 in the synaptic transmission of visual cortex is not clear. This study aimed to investigate the effect of group I mGluR on the synaptic transmission efficiency in the primary visual cortex of monocular deprivation amblyopia rat. Methods The 14-day-old rads were rangomly divided intonormal control group and form-deprivation group,with 8 rats in each group. The eyelids of the left eye were sutured to establish the monocular form- deprivation amblyopia rat model,The rats visual cortex slices were prepared and incubated in artificial cerebrospinal fluid . Four groups of drugs that it is 3,5-dihydroxyphenylglycine(DHPG), LY367385, 2-methyl-6(phenyl acetylene) pyridine hydrochloride(MPEP) and DHPG, LY367385and MPEP and DHPG were added to every group, respectively.The extracellular recording technique was used to record the field excitatory postsynaptic potential (fEPSP) in the visual cortex. Results: After application of DHPG, the fEPSP-slope of the visual cortex was significantly increased in both normal rats and monocular deprivation amblyopia rats ($P<0.001$), but the increase of normal group was significantly higher than that of amblyopia group ($P<0.05$). Application of LY367385, a selective mGluR1 blocker or Application of MPEP, an mGluR5 blocker can partially reduce the DHPG-induced fEPSP-slope in both normal group and amblyopia group. Conclusions:These results demonstrate that the effect of modulation of group I mGluR (mGluR1, 5) on the synaptic transmission was reduced in the visual cortex of monocular deprivation amblyopia rat. found that agonist DHPG of Group I mGluRs increased synaptic transmission efficiency of neurons in visual cortex of normal rats and monocular form deprivation rats.

Background

Human perceive the colorful world through the visual system, and more than 80% of outside information is received by visual system. The visual development depends on age and experience [22, 17,7,14]. The most sensitive period of visual development is called the critical period, in which abnormal visual experience or visual form deprivation such as strabismus, congenital cataracts and anisometropia [1,8,10] will lead to the occurrence of amblyopia, for which no organic cause can be detected on routine ophthalmic examination [8, 10]. But now the pathogenesis of amblyopia is not completely understood. Huber and Wiesel (1963) first proposed the view that visual system has plasticity during the critical period of the visual development [5], which is currently a hotspot for the pathogenesis research of amblyopia. Glutamate is the most abundant neurotransmitter in brain, acting on its receptor including mGluRs and modulating synaptic transmission and plasticity of visual system [20, 23,16,24], auditory cortex [19], hippocampus [21, 11,13,], olfactory bulb [3]. mGluRs, a super family of G-protein-coupled receptor, are classified as three groups, namely group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8) receptors [2,25]. Group II and III mGluRs were involved in the negative feedback regulation of the release of glutamate and positive regulation of the release of

GABA, inhibiting synaptic transmission [28]. In contrast, group I mGluRs increased the synaptic transmission [28,13].

The monocular deprivation (MD) is a classical paradigm for the exploring of experience- dependent plasticity [6]. Studies have confirmed that metabotropic glutamate receptor 1 (mGluR1) expression was decreased in visual cortex of MD amblyopia rats [29], but functional significance remains unclear. Exploring the mechanism of group I mGluRs on synaptic modulation is essential for the understanding of pathogenesis and pathophysiological processes of amblyopia.

Our study aimed to investigate the effects of group I mGluRs agonist DHPG on neuronal synaptic transmission of visual cortex of normal and monocular deprivation amblyopia rat by the electrophysiological methods and to provide clues to the pathogenesis of amblyopia.

Methods

Animals

16 standard Sprague-Dawley rats of 14 days after brith (From Beijing Vitonglihua Laboratory Animal Technology Co., Ltd. license No.), Average weight 30 grams, either sex, were randomly divided into two groups: the normal control group (NC group) and the monocular deprivation group (MD group). According to the application of different drugs, then the rats were subdivided into four groups: in NC1 and MD1 group, the drug DHPG was applied only; in NC2 and MD2 groups, we added the drugs DHPG and LY367385; in NC3 and MD3 groups, we applied the drugs DHPG and MPEP, while in the NC4 and MD4 groups, we added the drugs LY367385, MPEP and DHPG together. The rats were raised under the condition with food and water free intake, and maintained room temperature 23 °C ± 3 °C, humidity45–65%, and 12 h light/12 h dark cycle. In this study, the experimental protocols were approved by the ethical committee of the Animal Care and Experimental Committee of the Third Affiliated Hospital of Xinxiang Medical University. All experiments were in accordance with the Association for Research in Vision and Ophthalmology (ARVO) statements for ophthalmic research animal use. and all efforts were made to minimize animal suffering and reduce the number of animals used. Rats were euthanized by intraperitoneal injection of lethal 10% chloral hydrate （LD50）5ml/100g）,Rats showed respiratory depression, arrhythmia, and then cardiac arrest.

MD Model

8 Rats were anesthetized with 10% chloral hydrate (0.3ml/100g). eyelids were disinfected by Iodophor. Rats' left eyelids were sutured with interrupted horizontal mattress suture technique using 6-0 ophthalmologic surgical line. In order to prevent infection, erythromycin eye ointment was was applied on eyelids for 7 days after surgery. The rats with any eye lid reopening or corneal opacity during deprivation

period were discarded to euthanasia . All rats were reared to 50 days or older for the electrophysiological experiments.

Slice preparation

All rats were anesthetized with 10% chloral hydrate (0.3ml/100g), and perfused with 0℃cutting-ACSF, which consisting of (mM) 225 Sucrose, 3 KCl, 6 MgS04, 1.25 NaH2P04, 24 NaHC03, 0.5 CaCl2, 10 Glucose, through the left ventricle until the limbs turned white. Coronal visual cortex slices were cut (400μm) using a Leica VT1000S vibratome (Leica Microsystems UK, Milton Keynes, UK), and for MD group, only the right side visual cortex slices were selected. The primary visual cortex was identified according to a rat brain atlas [18]. ACSF contained (mM) 126 NaCl, 3 KCl, 2 MgS04, 1.25 NaH2P04, 24 NaHC03, 2CaCl2, 10 Glucose [27].

Electrophysiology

The extracellular microelectrode recording of brain slices were adapting a temperature controlled (30-32℃) interface-style bath perfusion system. Slices were submerged in the recording chamber, and perfused with ACSF (ph: 7.35-7.5, 30-32℃, a low rate of 3- 4ml/min), which is filled with a mixed gas (95%O2+5%CO2). The slices were allowed to equilibrate in this medium for 1h prior to recording. Recording electrode, were filled with ACSF (resistance 2–5 MΩ) and positioned in layer IV of visual cortex V1. Field excitatory postsynaptic potentials (fEPSPs) were evoked from a pulse stimulator (Master-9, AMPI Ltd., Israel) by a brief square current pulse (200μs) to the underlying layer 4 at a site in the middle of the visual cortex using a self-made stimulating electrode (150μm in diameter, Nichrome wire). The baseline response was obtained at 10s intervals for at least 10 min with a stimulus intensity that was yielded to a-half maximal amplitude of the test EPSP [12,7]. The change of fEPSP slope recorded after 10 min of optimal stimulus stabilization was used as an index to evaluate synaptic transmission efficiency.

Data acquisition and analysis

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 mains supply was eliminated from extracellular recordings online with the use of 50 Hz noise eliminators (HumBug; Digitimer Ltd.). Data were analyzed off-line using software from Spike 2 (CED, Cambridge, UK). All statistical tests were performed using SigmaStat software (SPSS Inc., California, USA). Results are expressed as means ± standard error of mean, unless indicated otherwise. Statistical significance for comparison between two groups or more than two groups was determined

using tests described in the text or in the figure legends, as appropriate. Measures were considered statistically significant, if $P < 0.05$.

Drugs used for electrophysiology

In all experiments, drugs were bath-applied after the baseline response being stable for at least 10min. All standard reagents including (s)-3,5-dihydroxyphenylglycine (DHPG), (+)-2- methyl-4-carboxyphenylglycine (LY367385) and 6-mephyl-2-(phenylethynyl) pyridine (MPEP), except where indicated, were obtained either from Sigma-Aldrich (UK) or VWR International (Lutterworth, UK). 2,3,-dioxo-6-nitro-1,2,3,4-tetrahydroben-zo[f]quinoxaline-7- sulphonamide (NBQX) was purchased from Tocris Cookson Ltd (Bristol, UK). The stock solution is diluted 103 times with water and used for working concentration. except for NBQX which was dissolved in dimethylsulphoxide and stored in individual aliquots at - 20℃. Working solutions were prepared freshly on the day of the experiment.

Results

The effects of DHPG on fEPSP recorded in V1 visual cortex from normal and monocular deprivation amblyopia rats. The stimulation-evoked fEPSP using certain intensity and duration in the V1 visual cortex was shown in figure 1A. Application of group I mGluR agonists DHPG (5μM) significantly increased the slope of postsynaptic potential (PSP) to 136.42±17.31% ($P<0.001$, versus self-control, n=8) (Fig1B, C). In order to determine whether DHPG-induced PSP is excitatory or inhibitory, we introduced the AMPA receptor antagonist NBQX. Application of NBQX (10μM) decreased rapidly the PSP slope (Fig. 1D), suggesting that DHPG- increased PSP is mainly mediated by the excitatory synapse in the rat visual cortex.

Figure 2 shows the changes of fEPSP slope in the visual cortex before and after application of DHPG at normal control (NC) and monocular deprivation (MD) rats. DHPG induced significantly increase in fEPSP slope in MD rats (120.72±12.77%, $P<0.001$, versus self-control, n=11); DHPG-induced fEPSP slope increase in MD rats was significantly smaller than that of NC group ($P=0.036$, versus NC group) (Fig 2). LY367385 and MPEP both reduce DHPG-increased fEPSP-slope partially in normal and amblyopia rats.

In order to determine whether group I mGluR subtypes (mGluR1and mGluR5) is involved in the mediation of DHPG-induced fEPSP, mGluR1 and mGluR5 antagonists LY367385 and MPEP were used in our experiments. The results show that LY367385 (100μM) can reduce DHPG-increased fEPSP-slope in the visual cortex of both NC and MD rats (NC with LY367385+DHPG 114.92±9.29%, n=5, $P=0.045$, versus NC with DHPG 136.42±17.31%; MD group with LY367385+DHPG 107.27±6.02%, n=6, $P=0.017$, versus MD group with DHPG120.72±12.77%; NC with LY367385+DHPG 114.92±9.29%, P□0.05, versus MD group with LY367385+DHPG 107.27±6.02%) (Fig 3A,B). These results suggest that mGluR1 was required for DHPG-induced fEPSP in both NC and MD rats.

Similar to the effect of LY367385, MPEP (25μM) decreased the DHPG-increased fEPSP- slope in the visual cortex of both NC and MD rats (NC with MPEP+DHPG 112.59±15.33%, n=8, P=0.005, versus NC DHPG 136.42±17.31%; MD with MPEP+DHPG 110.11±4.12%, n=7, P=0.045, versus MD with DHPG 120.72±12.77%; NC with MPEP+DHPG 112.59±15.33%, P□0.05, versus MD with MPEP+DHPG 110.11±4.12%) (Fig 4 A,B).

These results suggest that the activation of mGluR5 was also involved in the modulation of DHPG-induced fEPSP in both NC and MD rats.

As LY367385 or MPEP only partially blocked the role of DHPG, we tried to determine whether co-application of both mGluR1 and 5 antagonists can better block the role of DHPG. In accordance with our expectations, application of DHPG failed to increase fEPSP-slope for both NC and MD rats in the presence of both mGluR1 and 5 antagonists (NC with LY367385+ MPEP+ DHPG 104.51±2.15%, n=3, P=0.005, versus NC with DHPG 136.42±17.31%; MD with LY367385+ MPEP+ DHPG 102.83±14.92%, n=4, P=0.007, versus MD with DHPG 120.72±12.77%).

Discussion

The mammalian visual cortex V1 is primary visual cortex responsible for the processing of visual information, which constitutes the neural basis of perceptual activities. Anatomical and physiological characteristics of the visual cortex have been demonstrated ,The Layer IV of the visual cortex is mainly the termination of sensory nerve fibers. The layer IV of V1 visual cortex receive input from lateral geniculate nucleus and then projected onto the II, III, or V, VI layer, and further projected onto the other visual area or other cortex.

Cortical circuits are profoundly shaped by experience during postnatal development. The consequences of altered vision during the critical period for ocular dominance plasticity have been extensively studied in rodent primary visual cortex (V1). The critical period of rat visual development is 14 to 45 days after birth [4]. Postnatal rats for 12-14 days (eyes will start to, but not open), Monocular form deprivation mainly affects the visual afferent fibers, which significantly affects the fourth layer of the visual cortex. Tatti R[30] data also strongly suggest that experience plays a fundamental role in not only the maturation of synaptic transmission, but also its coordination across cortical layers. Have proved that 90% the optic nerve fibers cross to the opposite side at the optic chiasm in rat, and There was no significant difference in the expression of metabolic glutamate receptor 1 in bilateral visual cortex of monocular deprivation amblyopia rats [29]. so, in order to study the conduction function of visual cortex of MD rats, we just took the cortex opposite side of the sutured eye for the study.

DHPG enhanced a smaller fEPSP slope in MD rat, and mGluR1 and 5 similarly contribute to the modulation of DHPG on fEPSP slope. Normal visual stimulation is essential for the normal development of the visual cortex [8]. In this study, rat vision were deprived when they were in postnatal 12-14 days, a period their eyes still did not open yet, which may result in the abnormal development of visual system including decreased expression of mGluR1 receptor [29], decreased GluR binding sites and affinity to

GluR [15] and decreased synaptic transmission efficacy observed in this study. Previous studies also show group I mGluR agonist DHPG potentiate the ionic glutamate receptor subunits NMDA and AMPA receptor function in rat visual cortex [9], thus the decreased expression of group I mGluR may lead to the loss of the driving force of mGluR on the NMDA and AMPA receptor function, which may be another reason of impaired synaptic transmission efficiency in MD rats.

Both mGluR1 and mGluR5 antagonist reduced DHPG-induced fEPSP-slope, indicating that both the two mGluRs subtypes contribute to the modulation of synaptic transmission of visual cortex in normal and amblyopia rats, which can be verified by the result that co- application of both mGluRs antagonists completely blocked DHPG enhancement of fEPSP slope for both normal and MD rats. Our results are consistent with the observation of Volk et al [26]. That show both mGluR1 and mGluR5 participated in the hippocampal synaptic transmission and with the finding of Sidorov et al [24]. That demonstrate the involvement of mGluR5 in ocular dominance plasticity of rat using mGluR5-knockout rats.

Conclusions

We had generated amblyopia rat model by depriving rat vision in critical period of visual development, and found that agonist DHPG of Group I mGluRs increased synaptic transmission efficiency of neurons in visual cortex of normal rats and monocular form deprivation rats. Both antagonists which the LY367385 of mGluR1 and MPEP of mGluR5 partially antagonized the increased synaptic transmission efficiency of DHPG, and there was no significant difference between them. Our study may underlie an important mechanism of poor vision in MD amblyopia model.

Abbreviations

MGLUR: Metabotropic glutamate receptor

fEPSP: Field excitatory postsynaptic potential

DHDP: 3,5-dihydroxyphenylglycine

LY367385: 2-methyl-4-carboxyphenylglycine

MPEP: 2-methyl-6(phenyl acetylene) pyridine hydrochloride

ACSF: Artificial cerebrospinal fluid

MD: monocular deprivation NC: normal control

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Third Affiliated Hospital of Xinxiang Medical University and was performed in accordance with the principles of the Declaration of Helsinki.

All animal procedures conformed to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and The use and breeding of laboratory animals shall follow the Regulations on the Administration of Laboratory Animals promulgated by the Ministry of Science and Technology of China. (Animals are provided by Beijing of China Vitonglihua Laboratory Animal Technology Co., Ltd. Number:11400700217027)

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

XLL and CBL designed the study. RZ and JLW performed the experiment in rats .RZ,ZXS and LZ collected the data. JJL and YC analyzed and interpreted the data. XLL was a major contributor in writing the manuscript. XLL and RZ participated in drafting the manuscript. RZ and CBL revised the manuscript. All authors read and approved the final manuscript.

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Publisher’s Note

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Figures

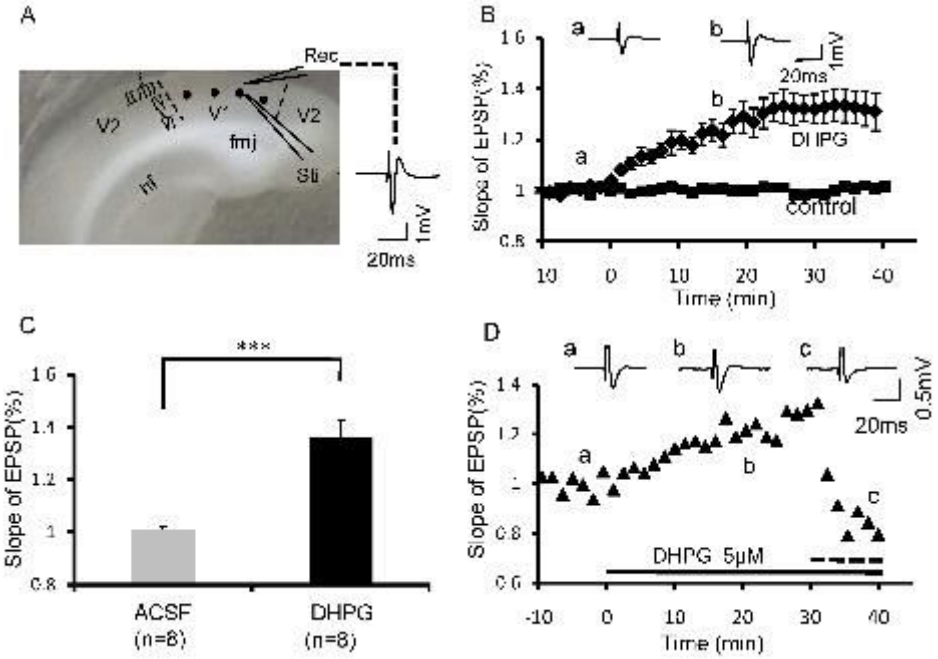

Figure 1

DHPG induced excitatory postsynaptic potential in the rat visual cortex. (A) A photo of a coronal slice cut from an adult rat brain at 6.04mm posterior of bregma and 2.96mm posterior of interaural. Black filled circles indicate the layer IV of visual cortex, Rec: the recoding electrode located at layer III, Sti: the stimulating electrode located at layer IV. V1: primary visual cortex. V2: secondary visual cortex. fmj: forceps major of the corpus callosum. hf: hippocampal fissure. The drawing at right side is one example of fEPSP trace. (B) The effects of DHPG on PSP. The line with rhombus represents time-effect curve of application of DHPG, the time of DHPG application is at 0min (n=8); the line with square represents time-effect curve of control in the absence of any agonist. The fEPSP traces at specific time points (a: control, b: DHPG) were displayed in the top panel of Fig1B. (C) The bar graph summarizes the percent change of fEPSP slope at control (gray bar) and DHPG group (black bar). ***p<0.001. (D) The effect of NBQX on DHPG-induced PSP change (%). The dotted line indicates the application of NBQX. The fEPSP traces at specific time points (a: control, b: DHPG, c: DHPG+NBQX) were displayed in the top panel of Fig 1D.

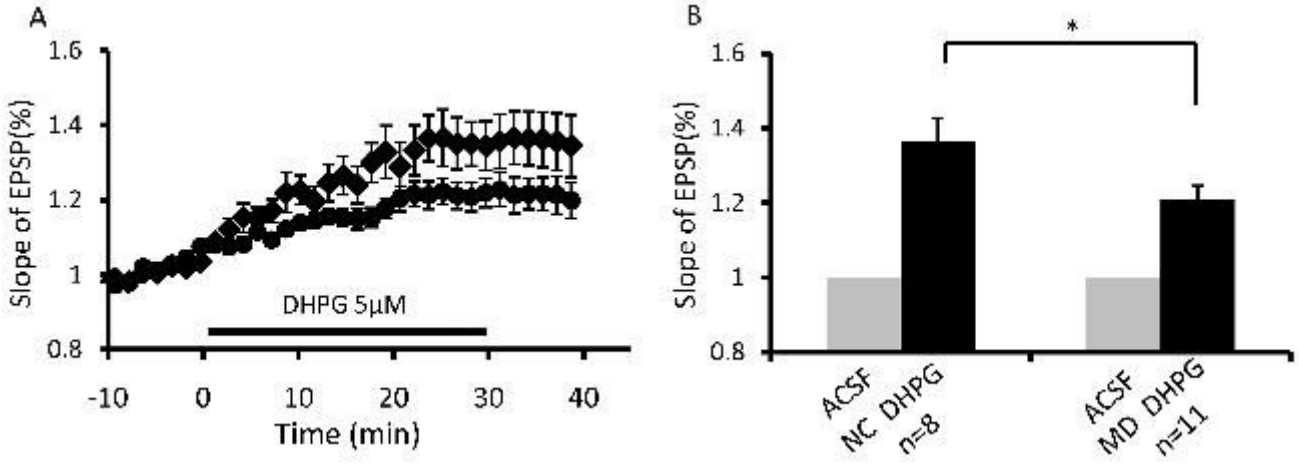

Figure 2

The effects of DHPG on fEPSP slope of visual cortex in NC and MD rats. (A) The time-effect curve of fEPSP slope before and after application of DHPG (5μM) in NC (black rhombus) and MD rats (black solid circle). (B) Bar graph summarizes the percent changes (%) of fEPSP slope after application of DHPG (5μM) in NC and MD rats.

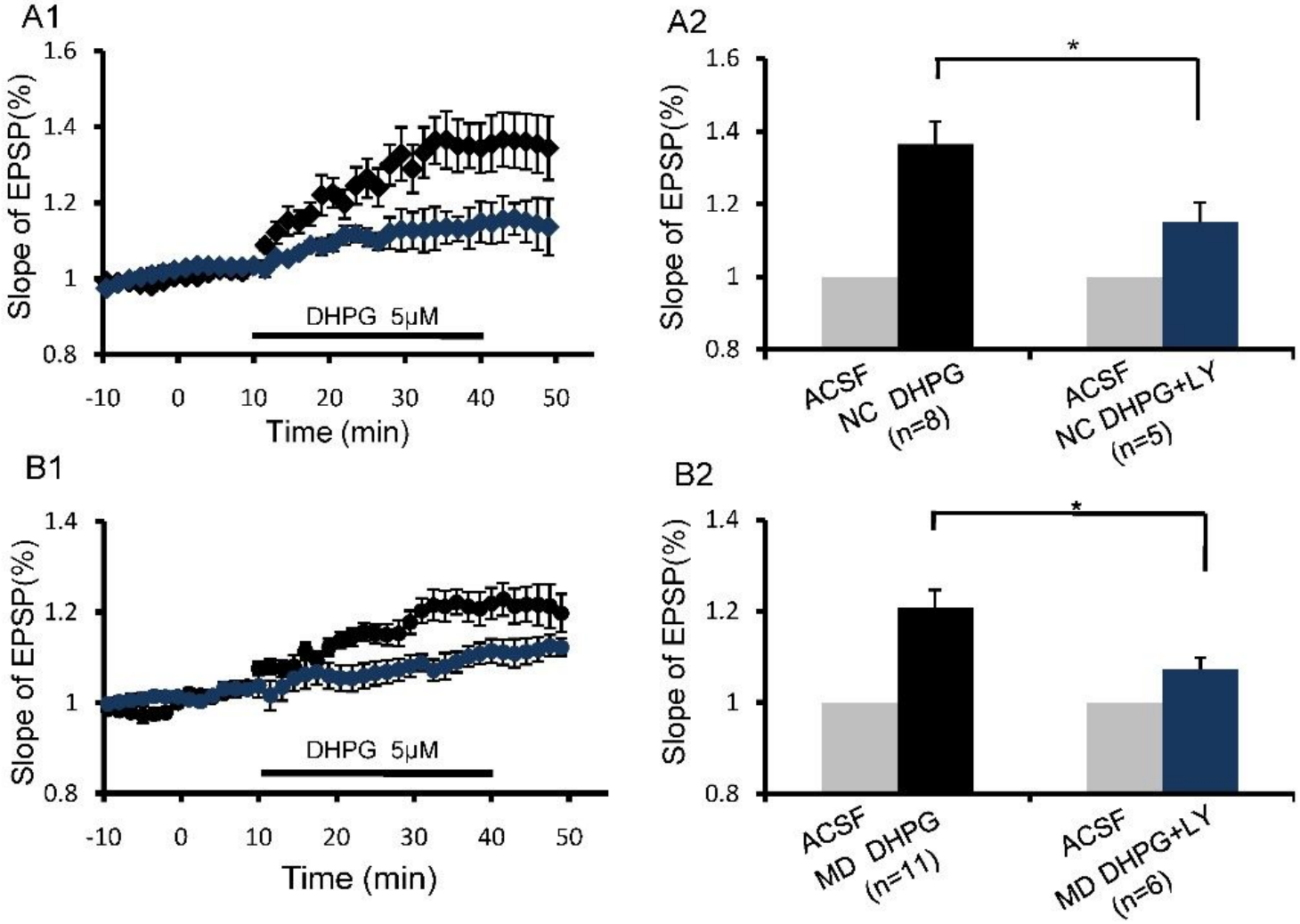

Figure 3

The effects of LY367385 on DHPG-induced fEPSP slope of visual cortex in NC and MD rats. (A1, B1) The time-effect curve of DHPG-induced fEPSP slope in the pretreatment of LY367385 in NC rats (A1) and MD rats (B1).Black rhombus and solid circle: application of DHPG (5μM) alone; blue rhombus and solid circle: application of LY367385 (100μM) + DHPG, the time of LY367385 application is at 0min. (A2, B2) Bar graph summarizes the percent changes (%) of DHPG-induced fEPSP slope in the pretreatment of LY367385 in NC rats (A2) and MD rats (B2). *p<0.05.

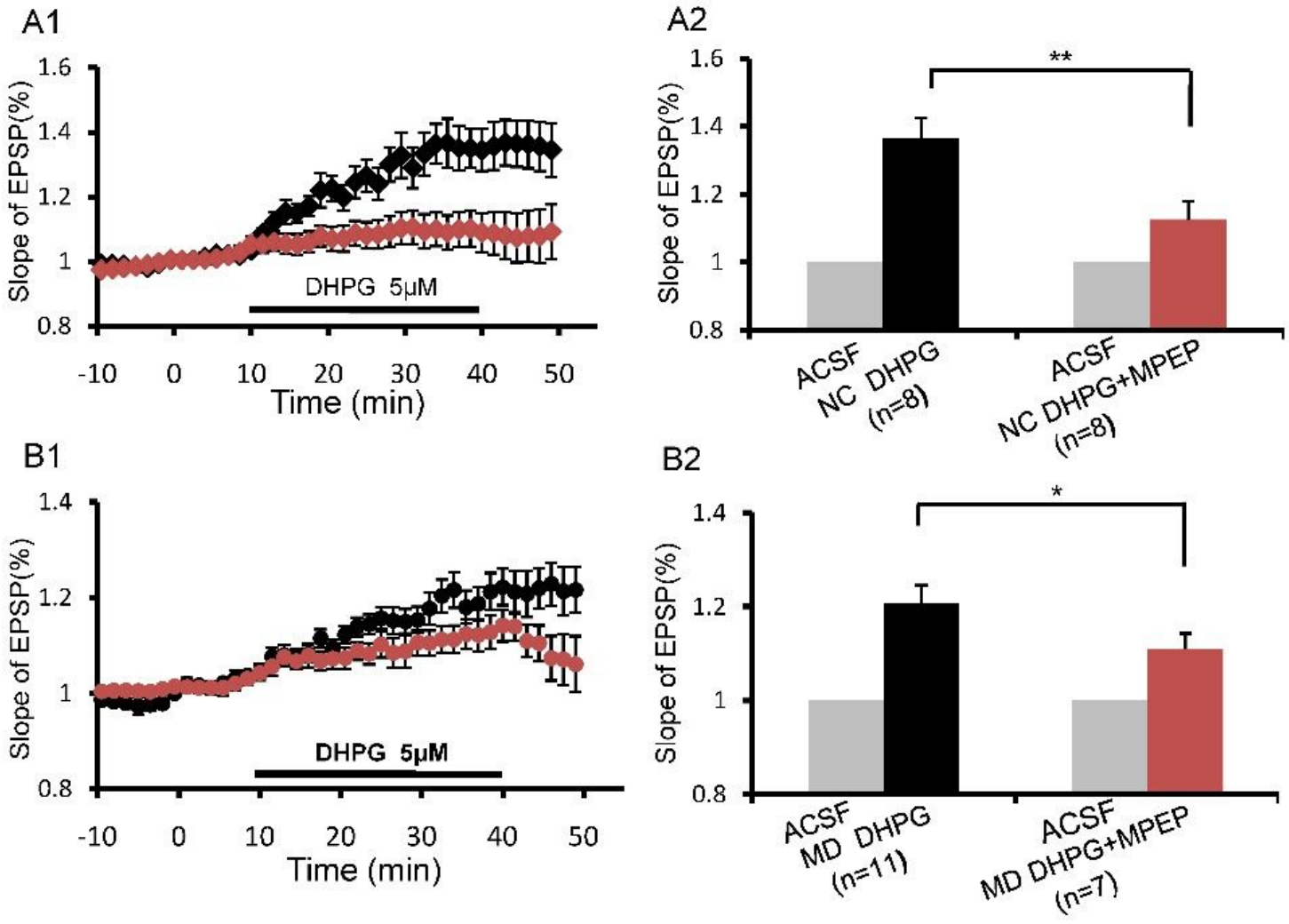

Figure 4

The effects of MPEP on DHPG-induced fEPSP slope of visual cortex in NC and MD rats. (A1, B1) The time-effect curve of DHPG-induced fEPSP slope in the pretreatment of MPEP in NC rats (A1) and MD rats (B1). Black rhombus and solid circle: application of DHPG (5μM) alone; red rhombus and solid circle: application of MPEP(25μM)+DHPG, the time of MPEP application is at 0min. (A2, B2) Bar graph summarizes the percent changes (%) of DHPG-induced fEPSP slope in the pretreatment of MPEP in NC rats (A2) and MD rats (B2). **p<0.01, *p<0.05.

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