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GABA INCREASES STIMULUS SELECTIVITY OF NEURONS IN PRIMARY VISUAL CORTICES OF CATS CHRONICALLY TREATED WITH MORPHINE

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Abstract—Chronic exposure to opiates leads to maladaptive changes in various functions of the mammalian brain, including properties of neuronal response in the visual pathway. In the present study, we used multibarreled microelectrodes to study the effects of electrophoretic application of GABA or the $GABA_A$ receptor antagonist bicuculline on the properties of individual V1 neurons in cats which were chronically treated with morphine (MTCs) or saline (STCs). The results showed that the application of either GABA or bicuculline significantly altered spontaneous activity as well as orientation selectivity and signal-to-noise ratios of visually evoked responses in both MTCs and STCs. While administration of bicuculline exerted a much stronger effect on neuronal responses of V1 neurons of the STCs, administration of GABA resulted in improved visual function mainly in MTCs. Most importantly, GABA-treated cells in area V1 of the MTCs displayed similar responses to those in STCs. These results are consistent with the idea that: (1) there is a decrease in GABA-mediated inhibition in area V1 of cats exposed chronically to morphine, and (2) this decrease contributes strongly to the apparent degradation of neuronal function observed in animals exposed chronically to morphine.

Key words: primary visual cortex, orientation selectivity, GABA, bicuculline.

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Abbreviations: BMI, bicuculline methiodide; CRT, cathode ray tube; EEG, electroencephalograph; FFT, fundamental Fourier component; LGN, lateral geniculate nucleus; LTP, long-term potentiation; MTC, morphine-treated cats; OB, orientation bias; PSTH, Post-stimulus time histogram; SEM, standard error of the mean; STC, saline-treated cats; STN, signal-to-noise ratio.

INTRODUCTION

Opiate abuse is an important social and medical problem throughout the world. It has been suggested that exposure to opiates may not only result in physical and psychological dependence but may also lead to many other behavioral changes, such as reduced visual sensitivity (Rothenberg et al., 1979) in humans, disordered behavior responses in kittens (Burgess and Villablanca, 2007), abnormal visual discrimination performance in rats (Grilly et al., 1980), and disrupted visual sensitivity in pigeons (Nielsen and Appel, 1983). Widespread maladaptive changes in neuronal structure and response properties (Rothenberg et al., 1979; Di Chiara and North, 1992; Robinson and Kolb, 1997, 1999; Pu et al., 2002; Wang et al., 2006; Li et al., 2010) induced by opiate exposure are thought to be the substrate of these disrupted behaviors.

Previous studies in our laboratory have revealed that, when compared with normal or saline-treated cats, cats treated chronically with morphine exhibit significantly different neuronal response properties, such as higher spontaneous activities, higher visually evoked responses and lower signal-to-noise ratios in both the lateral geniculate nucleus (LGN) (He et al., 2005a) and V1 (He et al., 2005b). A degraded signal-to-noise ratio leads to decreased ability of the neural system to discriminate signal from background, which therefore may have some relationship with the disrupted visual functions, such as the reduced visual sensitivity, described above. Additionally, decreased response modulation, extended time course of response and visual response latencies were also found in the visual pathway of cats given chronic morphine treatment (He et al., 2005c; Long et al., 2008). Most notably, orientation and direction selectivity, which play important roles in the perception of form (Hubel, 1988) and motion (Albright and Stoner, 1995),were also found to be impaired in the LGN (He et al., 2005a) and V1 (He et al., 2005b). All these findings suggest that chronic morphine exposure has a substantial influence on neurons in the visual pathway. Although a number of studies have proved that opiate receptors are expressed extensively in the visual system (Wise and Herkenham, 1982; Lewis et al., 1983; Walker et al., 1988), and that chronic opiate exposure results in morphological changes in neurons in the visual cortex (Li et al., 2007b;

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Hu et al., 2008), the precise mechanism by which chronic opiate exposure affects the functions of neurons in the visual system remains an open question.

It has been shown that chronic opiate exposure significantly affects various neurotransmission systems, including the glutamatergic (Martin et al., 1999a,b; Pu et al., 2002; Zeng et al., 2006) and GABAergic systems (Vaughan et al., 1997; Cruz et al., 2004; Laviolette et al., 2004; Li et al., 2007a; Madhavan et al., 2010). It is known that GABA plays an important role in the maintenance of neuronal performance in the visual pathway. Decreased GABA-mediated inhibition often leads to a decline in function of neurons involved in signal-to-noise ratio, orientation and direction selectivity (Eysel et al., 1990, 1998; Sato et al., 1996; Crook et al., 1997; Liu et al., 2007). On the basis of these findings, we hypothesized that chronic morphine exposure results in a decrease in GABA-mediated inhibition in area V1, which contributes to the apparent degradation of neuronal functions described above. As shown in a previous study (Leventhal et al., 2003), a simple way to test this hypothesis is to explore the effects of administration of GABA and bicuculline, a type of $GABA_A$ receptor antagonist, on neuronal function. If the proposed hypothesis is true, GABA administration would result in greater improvement in neuronal function in chronic morphine-treated cats (MTCs) while the application of bicuculline would exert a much stronger effect on neuronal responses in saline-treated cats (STCs). We therefore used multi-barreled microelectrodes to study the effects of electrophoretic application of GABA and bicuculline on the response properties of individual V1 cells in MTCs and STCs. Our findings provided strong support for the hypothesis.

EXPERIMENTAL PROCEDURES

Animals and morphine exposure

The experiments were performed on seven healthy adult male cats (2–3 kg), three of which comprised the morphine-treated group; the remaining four cats were used as a control saline-treated group. The protocol for morphine treatment was identical to that described previously (Pu et al., 2002; He et al., 2005a,b,c). Morphine HCl (10 mg/kg) was administered by cervical subcutaneous injection twice per day at 9:00 AM and 9:00 PM for 10 days before the electrophysiological experiments. Saline-treated cats were treated similarly, except that the saline (0.9%) was used. During the recording procedure, morphine or saline was injected in the same way.

All cats were examined using an ophthalmoscope before the experiment to ascertain that they had no optical defects or obvious retinal problems that would impair their visual function.

This study was performed in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocol was approved by the Committee on the Ethics of Animal Experiments of the University of Science and Technology of China.

Preparation for recording

On the 11th day, the animals were prepared for extracellular single-cell recording. The methods of preparation and single-cell recording have been described previously (Shou et al., 1996; Hua et al., 2006; Li et al., 2008). Cats were anaesthetized prior to surgery with ketamine HCl (20 mg/kg, intramuscular injection); following this, intravenous and tracheal cannulae were inserted. After surgery, each animal was placed in a stereotaxic apparatus. A long-acting anesthetic (1% lidocaine HCl) was applied to all wound margins and pressure points. The nictitating membranes were retracted using neosynephrine (0.5%). The pupils were dilated maximally with atropine, and contact lenses were used to protect the eyes from desiccation. A mixture of urethane (20 mg/kg/h) and gallamine triethiodide (10 mg/kg/h) was infused intravenously to maintain anesthesia and paralysis. The heart rate (about 180–220 pulses/min) and electroencephalograph (EEG) were monitored to assess the level of anesthesia. End-expiratory CO_2 was maintained at approximately 4%; body temperature was maintained at 38 °C. A craniotomy (8 mm diameter) was performed 4 mm posterior to the ear bars in the midline, and the dura was removed. We also used published visuotopic maps of areas 17 (Tusa et al., 1978) to identify the areal location of cells. After introduction of the electrode assembly, the opening was covered with a 4% solution of agar in saline. Action potentials of isolated cortical cells were recorded extracellularly using microelectrodes with impedances of 2–5 MΩ (filled with 4 M NaCl).

Visual stimulation

The visual stimulation was identical to that used previously (Li et al., 2008). Computer-controlled visual stimuli were generated on a gamma-corrected Sony G220 CRT monitor (1024 × 768, 100 Hz), placed 57 cm from the eyes of the cats. The mean luminance of the display was 45.2 cd/m^2, and the environmental luminance on the cornea was approximately 0.1 lux. The program that generated the stimulus was written in MATLAB (Mathworks, Natick, MA, USA), using the extensions provided by the high-level Psychophysics Toolbox (Brainard, 1997) and low-level Video Toolbox (Pelli, 1997). We used drifting sinusoidal gratings as stimuli (2 Hz), at five cycles per trial (2.5 s). The Michelson contrast of the stimuli was 99%. Each stimulus orientation was presented in two trials for a total of 10 cycles/orientation. Blanks (4 s) of the same mean luminance as the grating stimuli were interleaved with stimulus trials to determine the spontaneous firing rate and to prevent response adaptation. We selected an optimal stimulus size and spatial frequency for each cell during stimulation of the dominant eye. Subsequently, a set of sinusoidal gratings with optimal stimulus parameters, moving in 24 different directions (0–345° scale with an increment of 15°) was used to compile the orientation tuning curves. The direction of movement of each stimulus was orthogonal to its orientation.

Drug application

The methods of application of GABA and bicuculline were the same as used generally before (Leventhal et al., 2003; Li et al., 2008) GABA and bicuculline were delivered through multibarrel electrode arrays containing four pipette channels. Two of the barrels were used to hold GABA and bicuculline, one was filled with NaCl (4 M) to record the action potentials of the cells and the final barrel was filled with vehicle solution (pH 4.5) to balance the current. The following drug solutions were prepared for each experiment: GABA (0.5 M, pH 3.5) and bicuculline methiodide (BMI; 5 mM, pH3.5). All solutions for use in the microiontophoresis were prepared immediately before the experiments, filtered, and kept at 4 °C for subsequent use. Administration of one drug at a time was accomplished by passing +20 to +50 nA through the barrel. Mean and standard error of the mean (SEM) of ejecting currents of GABA and BMI in MTCs were 47.70 ± 0.83 nA (mean ± SEM) and 47.03 ± 0.96 nA, and in STCs were 48.24 ± 0.69 nA and