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Research Report

Chronic morphine exposure affects the visual response properties of V1 neurons in cat

Lihua He[a], Xiangrui Li[a], Tianmiao Hua[a], Pinglei Bao[a], Rui Ma[a], Yifeng Zhou[a,b,*]

[a]*Hefei National Laboratory for Physical Sciences at Microscale and School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, P.R. China*
[b]*State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Science, Beijing 100101, P.R. China*

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Abstract

Chronic opiate exposure leads to maladaptive changes in brain function. In view of the localization of opiate receptors in mammalian visual system, chronic opiate exposure is likely to affect the visual responses properties of V1 neurons. Using in vivo single-unit recording, we here showed that chronic morphine treatment resulted in the functional abnormality of primary visual cortical cells. When compared with saline-treated (as control) cats, cortical neurons in morphine-treated cats exhibited higher spontaneous activity, lower signal-to-noise ratios and weaker orientation and direction selectivity. However, re-exposure with morphine could significantly improve the function of V1 neurons in morphine-treated cats. These findings demonstrated that chronic morphine treatment could significantly degrade the response properties of V1 neurons and may lead to a function dependence on morphine in visual cortical cells.

Theme: Sensory systems
Topic: Visual cortex: striate

Keywords: Direction selectivity; Orientation selectivity; Signal-to-noise ratio; Spontaneous activity; Visual cortex

1. Introduction

The brain is rich in opiate receptors and significant concentrations of opiate receptors are observed in the visual system of cat [52], macaque [54] and rat [29], which suggests that visual system is subject to opiate modulation. Previous studies showed that morphine-like drugs decreased visual sensitivity in humans [41], and affected visual discrimination performance in rats [17] and cortical potentials evoked from optic chiasm stimulation in cats [53]. Our recent work also showed that chronic morphine exposure led to degradation of response modulation of visual cortical cells in cats [19].

Moreover, normal excitatory and inhibitory synaptic transmission is crucial for the development and maintenance of visual cortical function. It has been shown that chronic exposure to opiates significantly change glutamatergic synaptic transmission and neuronal plasticity in hippocampus [18,31,37], nucleus accumbens [32–34], periaqueductal grey [49] and other brain regions [1,2,20,55]. Similarly, GABAergic synaptic transmission is also influenced by opiates [10,11,26,50]. These findings indicate that opiates might result in the functional degradation of visual cortex. In the present study, we tested this possibility by using extracellular single-unit recording techniques to examine the stimulus selectivity of V1 neurons in chronic morphine-treated cats.

Abbreviations: MC, morphine-treated cat; Control, saline-treated cat; OB, orientation bias; DB, direction bias; SA, spontaneous activity; STN, signal-to-noise ratio

* Corresponding author. School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, P.R. China. Fax: +86 551 3607014.
E-mail address: zhouy@ustc.edu.cn (Y. Zhou).

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2. Materials and methods

2.1. Subjects and drug exposure

The experiments were performed on 11 healthy adult male cats (2–3 kg), 5 of which were used as morphine-treated group and 6 were used as control. All animal treatments were strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The protocols of morphine treatment were similar to those used by other researchers [14,37,47]. Morphine HCl (10mg/kg) was administered by cervical subcutaneous injection twice per day at 9:00 AM and 9:00 PM for 10 days before electrophysiological experiments. Control cats were treated similarly by saline instead of morphine.

All cats were examined ophthalmoscopically before the experiment to ascertain that they had no optical problems or obvious retinal problems that would impair visual function.

2.2. Preparation for extracellular recording

On the 11th day, the animal was prepared for extracellular single-unit recording as described previously [44,57]. Briefly, cats were initially anesthetized with ketamine HCl (20 mg/kg). Lidocaine (1%) was applied to all incisions of surgical entry. After the intravenous and tracheal cannulas were inserted, cats were placed in a stereotaxic apparatus. Pupils were dilated with atropine (1%), and nictitating membranes were retracted with phenylephrine HCl (5%). Eyes were protected with contact lenses and focused at a distance of 57 cm. A mixture of urethane (20 mg/hr/kg body weight) and gallamine triethiodide (10 mg/hr/kg) was infused intravenously to maintain anesthesia and paralysis. Expired CO_2 was tested by a CO_2 monitor (MULTINEX, USA) and maintained at approximately 4% by adjusting the respiratory rate and the inspired volume. Heart rate (about 180–220 pulses/min) and EEG were monitored throughout the experiment to evaluate the level of anesthesia. A small hole was drilled in the skull 4 mm posterior to the ear bar and 2 mm lateral to the midline. A tungsten-in-glass microelectrode (with an impedance of 2–3 MΩ) was positioned and advanced using a hydraulic microdriver (Narishige, Japan). The small hole was filled with a 4% solution of agar in saline and sealed with wax. The optic discs were projected on a tangent screen situated 114 cm away from the eyes of cats, and then the position of the area centralis was determined. Receptive fields were first hand-plotted using flashing and moving bars and classified as simple or complex cells [21]. Cells studied had receptive fields located within 8° from the area centralis. A typical recording lasted for 3 days. And during recording, morphine or saline was injected in the same way as described above.

At the end of the experiment, the cat was deeply anesthetized and perfused through the heart. Blocks of tissue containing the V1 area were removed and post-fixed for later morphological studies.

2.3. Visual stimulation

Computer-controlled visual stimuli consisted of drifting sinusoidal gratings were presented on a CRT monitor (1024 × 768, 85 Hz), placed 57 cm away from animal's eyes. The program to generate the stimulus is written in MATLAB, using the extensions provided by the high-level Psychophysics Toolbox [6] and low-level Video Toolbox [36]. We selected optimal stimulus size, temporal and spatial frequency of grating for each cell. Each stimulus was presented monocularly to the dominant eye. Then, a set of sinusoidal gratings with optimal stimulus parameters, moving in 24 different directions (0–360° scale with an increment of 15°) was used to compile the orientation and direction tuning curves. The orientation of each drifting stimulus was orthogonal to its direction of motion. Before each stimulus presentation, 5-s spontaneous activities were obtained while mean luminance was shown on the display. The contrast of stimulus was set at 80%. The mean luminance of the display was 19 cd/m^2, and the environment luminance on the cornea was 0.1 lx.

2.4. Data collection and analysis

After neuronal signal was amplified with a microelectrode amplifier (NIHON KOHDEN, Japan) and a differential amplifier (FHC, USA), action potentials were fed into a window discriminator with an audio monitor. The original voltage traces were digitized using an acquisition board (National Instruments, USA) controlled by IGOR software (WaveMetrics, USA). The original data were saved for later analysis.

The post-stimulus time histograms (PSTHs) of neuronal responses were obtained for further analysis. The responses of a cell to the sinusoidal gratings were defined as the amplitude of the fundamental Fourier component (FFT1) of the PSTH integrated over a time equaling to the stimulus modulation period. The FFT1 value of each stimulus orientation (direction) was used to draw the orientation (direction) tuning curve. The method for calculation of orientation bias and direction bias has been described elsewhere [28,43]. Briefly, the responses of each cell to different stimulus orientations or directions were stored as a series of vectors. The vectors were added and divided by the sum of the absolute values of the vectors. The angle of the resultant vector gave the preferred orientation or direction of the cell. The length of the resultant vector, termed the orientation or direction bias (OB or DB), provided a quantitative measure of the orientation or direction sensitivity of the cell. A cell with bias $\geq$ 0.1 was considered significantly biased for orientation or direction. And a cell with bias $\geq$ 0.2 was considered strongly biased for orientation or direction. A cell's signal-to-noise ratio (STN) was defined as the ratio of the cell's visual evoked response (FFT1 value in optimal direction) to spontaneous activity [12]. To avoid data skewing or overestimation, all

spontaneous activities below 1 spike per second were set equal to 1 spike per second for signal-to-noise analysis.

3. Results

3.1. Effect of chronic morphine treatment on orientation and direction selectivity

The results described here were obtained from 218 cells (125 complex cells and 93 simple cells) in 5 morphine-treated cats (abbreviated to MC 1 to MC 5) and 210 cells (114 complex cells and 96 simple cells) in 6 saline-treated cats (abbreviated to control 1 to control 6) in cortex area 17. Neurons recorded from each group of cats were at the same range of depth from the surface of the brain to avoid laminar bias. The comparison between two groups showed that complex and simple cells exhibited the similar effect of chronic morphine treatment, therefore the data of two-type cells were analyzed together.

MCs showed decreased orientation and direction selectivity relative to controls. OBs and DBs of cells of any individual MC were less than that of any individual control, though some of the differences were not significant. Before the physiological experiments, ophthalmologic examinations showed no difference between MCs and controls, indicating that the optical factors were not involved in the effect.

The OBs were significantly smaller in MCs (0.26 ± 0.17) than in control cats (0.38 ± 0.21; Mann–Whitney test and t test, $P < 0.0001$). These and analogous data are described as mean ± standard deviation, unless noted otherwise. Eighty-nine percent of cells in MCs and 97% of cells in controls showed significant orientation sensitivity (OB > 0.1). However, the percentage of cells with strong orientation selectivity (OB > 0.2) was lower for MCs (54.1%) than for controls (76.2%, Fig. 1). Furthermore, the percentage of cells that were highly biased for orientation (OB > 0.5) was lower for MCs (9.2%) than controls (26.7%). Similarly, direction selectivity of V1 cells was also affected by chronic morphine exposure. An analysis comparing the direction bias data for MCs vs. controls also showed that DBs of V1 cells were significantly less for MCs (0.18 ± 0.14) than for controls (0.26 ± 0.18; Mann–Whitney test and t test, $P < 0.0001$). As with orientation bias, the percentages of cells showing significant and strong direction bias in MCs (69.7% and 31.7%, respectively) were less than those in controls (81.0% and 50.5%, respectively). Cells of MCs are biased toward low selectivity values (Fig. 1A) while the values for the controls are distributed homogeneously (Fig. 1B). Eighty percent of cells in MCs were located in the range of OB < 0.37 and DB < 0.26, while for controls, the range extended to OB < 0.58 and DB < 0.37 (Figs. 1C and D). The results show that the strong response selectivity is missing in MCs, suggesting that chronic morphine exposure led to the degradation of orientation and direction selectivity of V1 cells in cats.

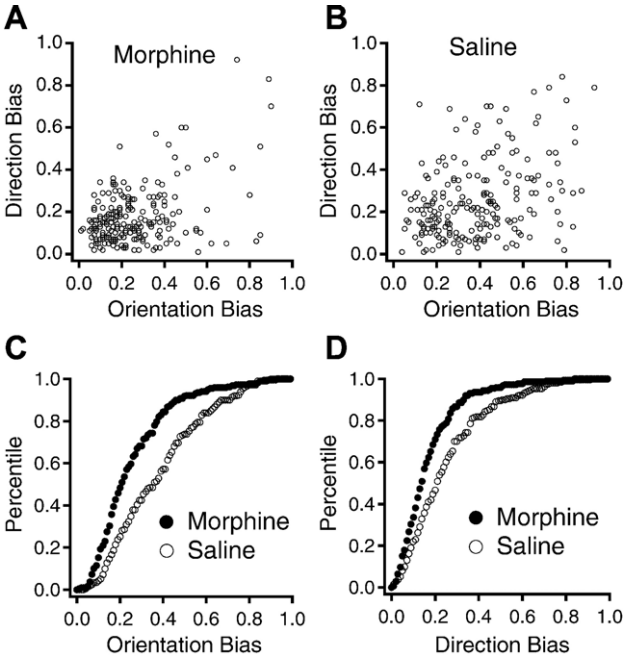

Fig. 1. Comparison of orientation and direction biases in V1 cells between morphine-treated (n = 5) and saline-treated (n = 6) cats. The total numbers of neurons are 218 for morphine-treated cats and 210 for saline-treated cats. The scatter plots (A, B) characterize the data from two groups. The cumulative distribution plots (C, D) show the percentile of cells with orientation or direction bias lower than a given value. It is clear that the cells in the morphine group show lower orientation and direction bias.

To explore whether the decreased selectivity of cells in MCs resulted from an increased responsiveness to previously non-optimal orientations and directions or from a reduced responsiveness to the previously optimal orientations and directions, or both, we analyzed the responses in preferred and non-preferred orientation or direction in V1 cells of MCs and controls. For the cells with significant orientation selectivity (n = 194 for MCs, 204 for controls), no difference of response in preferred orientation was found between MCs (15.2 ± 9.0) and controls (14.2 ± 10.1; Mann–Whitney test and t test, $P = 0.084$ and 0.26, respectively), but response in non-preferred orientation (orthogonal to preferred orientation) was significant higher in MCs (3.2 ± 3.3) compared with that in controls (2.0 ± 2.6; Mann–Whitney test and t test, $P < 0.0001$). Figs. 2A and B show the distribution of orientation-selective cells with responses in preferred orientation and non-preferred orientation, respectively. It is clear that the response in non-preferred orientation was affected by morphine exposure. Figs. 2C and D show the distribution for direction-selective cells (n = 152 for MCs, 170 for controls). The result is similar to orientation-selective cells. No difference of response in preferred direction was found between MCs (22.2 ± 14.3) and controls (21.2 ± 15.5; Mann–Whitney test and t test, $P = 0.23$ and 0.48, respectively), but response in non-preferred direction (opposite to preferred

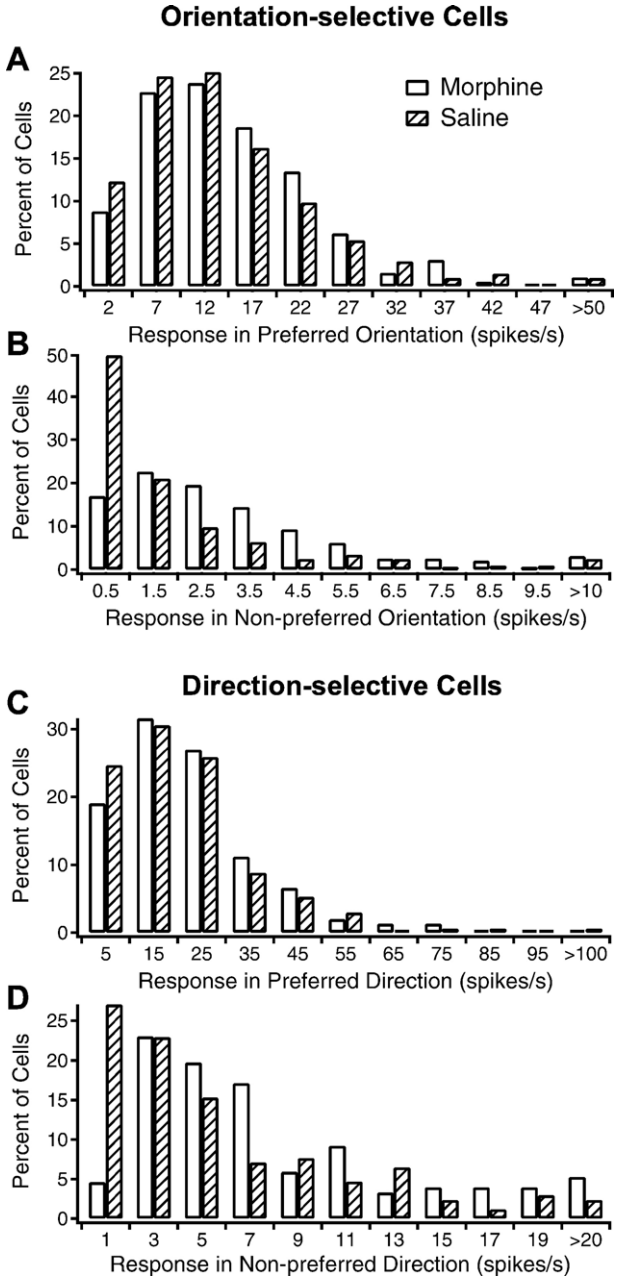

Fig. 2. Comparison of response in preferred and non-preferred orientation and direction between morphine-treated and saline-treated cats. There is no difference of responses in preferred orientation (A) and direction (C) between the two groups (t test, $P = 0.26$ and 0.48, respectively). But a significant increase of responses in non-preferred orientation (B) and direction (D) is found in morphine-treated cats compared with those in saline-treated cats (t test, $P < 0.0001$ and 0.01, respectively). This indicates that the degradation of orientation and direction selectivity in morphine-treated cats is due to the increase of response in non-optimal orientation and direction.

direction) showed a significant increase in MCs (8.5 ± 7.2) compared with that in controls (6.1 ± 7.4; Mann–Whitney test and t test, $P < 0.01$). These results suggest that an increased responsiveness to previously non-optimal orientations and directions contributes to the decreased selectivity of cells in MCs.

3.2. Effect on spontaneous activity and signal-to-noise ratio

We also analyzed the spontaneous activity (SA) of V1 neurons in two groups. V1 cells in MCs had significantly higher spontaneous activity compared with controls (10.3 ± 7.5 and 3.9 ± 4.5, respectively; Mann–Whitney test and t test, $P < 0.0001$). Multiple two-group comparisons of spontaneous activity were carried out between individual MC and control. With some exceptions (MC 3 and 5 vs. control 1 and 6), the average SA value for each individual MC was significantly higher than that of any individual control (t test, $P < 0.05$). Quite a number of V1 cells in controls (35.2%) had SA values less than 1 spike per second while the percent was much lower in MCs (5.0%). The percent of V1 cells showing SA value of > 5 spikes per second was two-fold greater for MCs (72.0%) than for controls (31.4%, Fig. 3A).

Due to the increased SA of V1 cells, MCs showed a decreased signal-to-noise ratio (STN; 4.3 ± 6.6) compared with controls (10.9 ± 10.3; Mann–Whitney test and t test, $P < 0.0001$; Fig. 3B). The percent of V1 cells having STN value less than 5.0 was lower (35.7%) in controls. Whereas, most V1 cells (78.9%) had STN value less than 5.0 in MCs. Similar to SA, the average STN value for each individual MC was significantly lower than that for any individual control except four pairs (MC 3 and 4 vs. control 1 and 6; t test, $P < 0.05$).

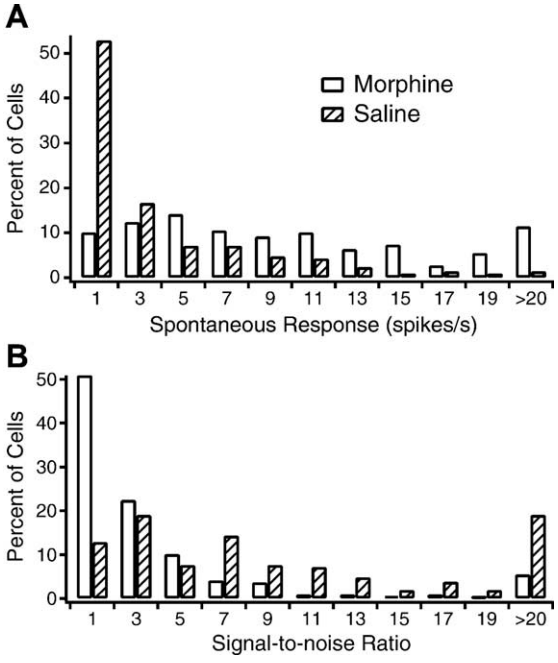

Fig. 3. Comparison of spontaneous activity and signal-to-noise ratio (STN) between morphine-treated and saline-treated cats. Neurons in morphine-treated cats show decreased STN (B) that mainly attribute to increased spontaneous activity (A).

3.3. Restoration of visual response properties by re-exposure to morphine

Chronic drug exposure leads to maladaptive changes of the nervous system to the drug. It is necessary for maintaining normal function to assimilate drug repeatedly [25]. As mentioned in Materials and methods, morphine was also injected at 9:00 AM and 9:00 PM everyday during the electrophysiological experiments. Our results showed that the response properties of V1 cells in MCs changed following a 12-h morphine exposure cycle. Compared with the cells (n = 45) recorded within 3 h before morphine injection, the cells (n = 46) recorded within 3 h after injection showed the increase of OB, DB and STN (t test, $P < 0.05$ for all), but left SA unchanged. In order to examine further the effect of morphine re-exposure on the visual responses properties of V1 cells, we recorded the response of the same cell after and before morphine re-exposure, and the response of 14 V1 neurons was successfully recorded in MCs after 10 min of morphine re-exposure.

Fig. 4 shows an example of direction-selective cell. The direction tuning curve becomes sharper after morphine injection, resulting in increased DB (from 0.37 to 0.48). We can also see that the increased DB is mainly due to the decreased response in non-preferred direction after morphine re-exposure. For all 14 cells, the response in preferred orientation kept unchanged after morphine re-exposure (14.9 ± 8.8 vs. 14.9 ± 11.4, paired t test, P = 0.87), so did the response in preferred direction (21.9 ± 13.4 vs. 20.6 ± 17.0; paired t test, P = 0.53). Whereas, both the responses in non-preferred orientation and direction were somewhat lower after re-exposure (2.7 ± 2.8 and 7.9 ± 6.9) than before (3.2 ± 2.8 and 9.2 ± 8.0), though the difference was not significant (paired t test, P = 0.11 and 0.23).

The response change of 14 cells before and after morphine re-exposure is summarized in Fig. 5. In Fig. 5A, most dots are placed above the line of slope 1, suggesting that orientation and direction selectivity is improved after morphine re-exposure. Eleven out of 14 cells show increased OB (paired t test, $P < 0.05$) and 12 of 14 cells show increased DB (paired t test, $P < 0.05$). Thirteen out of 14 cells showed higher STN (mean increase: 3.1) and another cell showed a small decrease of STN (9.4/9.3) after morphine re-exposure. But the difference is not significant (paired t test, P = 0.07; Fig. 5B). However, V1 cells (n = 3) in controls did not show the effect of acute morphine exposure on OB, DB or STN (paired t test, $P > 0.05$ for all).

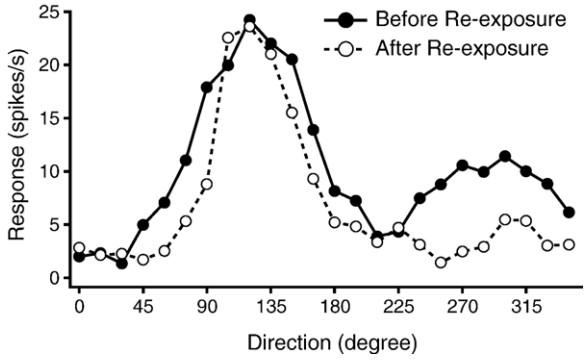

Fig. 4. Direction turning curves before and after re-exposure to morphine in a cell of morphine-treated cats. The DB value of this cell increases from 0.37 to 0.48 after morphine re-exposure, due to the decreased response in non-preferred direction.

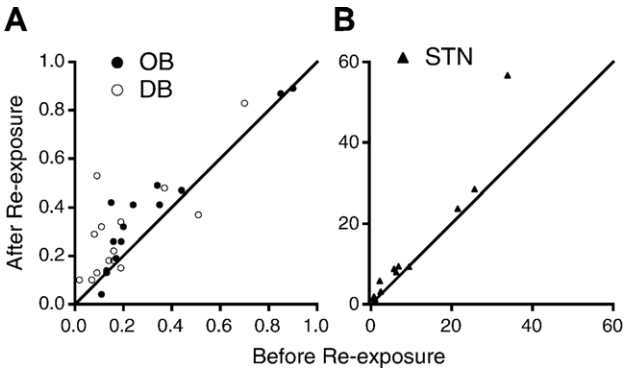

Fig. 5. Effect of morphine re-exposure on responsive properties of 14 cells in morphine-treated cats. (A) Scatter plot shows the change in orientation and direction bias. (B) Scatter plot shows the change in signal-to-noise ratio. Most cells are placed above the line of slope 1, and paired t test shows $P < 0.05$ for orientation and direction bias and P = 0.07 for signal-to-noise ratio, which suggest that re-exposure to morphine improves visual cortical function in morphine-treated cats.

4. Discussion

To our knowledge, this report is the first to describe the effect of chronic morphine exposure to the visual response properties of V1 neuron in the cat. The statistical data presented here suggested that chronic morphine treatment could lead to function decline of V1 neurons: decreased orientation and direction selectivity for visual stimuli and reduced signal-to-noise ratio (due to the increased spontaneous activity). This functional degradation, however, could be reversed by morphine re-exposure.

4.1. Results of physiological experiments

Our results show the systemic functional degradation of primary visual cortex in MCs. Chronic morphine exposure leads to the degradation of orientation and direction selectivity of V1 neurons. Average OB and DB values in MCs are significantly less than those in controls. Further analysis suggests that an increased responsiveness to non-optimal orientations and directions contributes to the decreased selectivity of cells in MCs.

One hypothesis is that inhibition reduces the response mainly in the non-preferred orientations and directions [4,5,15,16]. This hypothesis is supported by pharmacological studies which demonstrate that blockage of intracortical inhibition could markedly reduce stimulus selectivity

[9,13,39,42,45,46,48,51] and increase the spontaneous discharge rate [13,42] of V1 cells. Furthermore, Leventhal et al. reported that GABA-mediated inhibition degraded with age and that GABA and its agonists could decrease the spontaneous activity and improve the stimulus selectivity of V1 neurons which was poor in senescent monkeys [27]. It was reported that systemic morphine exposure could reduce GABA release [38]. And our resent work also indicated that chronic morphine exposure resulted in degradation of inhibitory neurotransmission of visual cortex in cat [19]. Therefore, it is likely that the decreased stimulus selectivity and increased spontaneous activity of neurons in MCs result from a general weakness of intracortical inhibition. Nonetheless, it should be mentioned that the increase of GABA release by chronic morphine exposure has also been reported [7,22].

Experiments by Eysel et al. [13] have shown that the blockage of inhibition led to an increase in the visual evoked response. Further evidence was found in aged monkeys whose neurons in primary visual cortex showed an increased responsiveness to not only non-optimal but also optimal orientations and directions due to the degradation of intracortical inhibition [27,43]. In our investigation, however, V1 cells of MCs showed increased responses only in non-preferred orientations and directions. By comparing these findings, we argue that the efficiency of excitatory synaptic transmission is diminished slightly in MCs, which is consistent with the conclusion of Martin et al. that the overall effect of chronic morphine should decrease glutamatergic transmission, exerted both presynaptically [34] and post-synaptically [33].

Altogether, the interaction of decreased excitation and decreased inhibition results in the degradation of orientation and direction selectivity in MCs. Nonetheless, we cannot the exclude possible effect of the amygdala in our results. The amygdala is involved in the circuits of addiction and is becoming the focus of interest in drug abuse research [8,24]. Moreover, it is known that the amygdala projects directly to the visual system, including V1, V2 and higher-level visual cortical areas [3]. But the types of synaptic connections are still unknown. Further study is needed to decide whether the projections from amygdala to visual cortex contribute to the functional degradation of primary visual cortex in MCs. Similarly, the input from lateral geniculate nucleus, which would also be influenced by chronic morphine exposure, might contribute to the degradation of response properties of V1 neurons in MCs. In addition, the role of other neurotransmitter systems cannot be ruled out. In particular, the dopaminergic and noradrenergic systems, which are implicated in the development of addiction [23,40], modulate the neuronal activity directly or indirectly by glutamatergic and GABAergic systems in the visual system [12,56]. But a few documents are still controversial about their role in the visual system. Interestingly, morphine re-exposure could improve the responses properties of V1 neurons in MCs, while the response of V1 neurons in controls was not affected by acute exposure of morphine. These results indicated that chronic morphine exposure led to some changes in subcellular lever, such as the cAMP pathway [35], which may make V1 neurons sensitive to morphine re-exposure.

4.2. Dependency of visual cortex on morphine

It is well known that chronic exposure leads to adaptation of the nerve system to opiates and that stopping opiate intake would break the balance and result in the dysfunction of the brain. In MCs, the similar unbalance was also found when comparing the response of V1 neuron in two phases of morphine exposure cycle. Therefore, to continuously obtain opiates is necessary for maintaining the relative normality of brain function. Our results show that the response properties of V1 neurons in MCs were improved by morphine re-exposure, which indicate that the function of visual cortex became morphine-dependent after chronic morphine exposure. Pu et al. [37] reported that the hippocampal function adapted to the presence of opiates after chronic opiate treatment. Considering the extensive expression of opiate receptors throughout the mammalian brain [30] and in visual system of cat [52], it is rational to speculate that such opiate dependency would take place in the visual system as well as in other brain regions.

4.3. Comparison with old animals

Experiments by Schmolesky et al. [43] have demonstrated the degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. These neurons exhibited higher evoked responses, higher spontaneous activities, lower signal-to-noise ratios and weaker orientation and direction selectivity compared with young ones. Here, we show that similar degradation of stimulus selectivity takes place in MCs. V1 neurons in MCs also show higher spontaneous activities, lower signal-to-noise ratios and weaker orientation and direction selectivity compared with control cats. So many similarities in functional decline of V1 neurons that existed in old and opiate-treated animals are surprising. Whether aging and opiate abuse share some processes in the degradation of nerve system is worthy of further investigations.

Based on plenty of information about structure and function of visual system and quantitative analysis to neuronal response, to explore the effect of opiate abuse on the function of visual cortex will be, we think, beneficial to the understanding of the systematic influence of drug abuse and its underlying mechanisms as well as the role of opiate receptors in the visual system. We speculate that the decrease of excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission results in the degradation of stimulus selectivity of visual cortical cells in MCs. However, other transmitter systems might also contribute

to the decreased selectivity of visual cortical cells. Additional studies are needed to clarify the mechanism mediating the degradation of function of the visual system in animals suffering chronic opiate exposure.

Acknowledgments

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