Neuroscience 226 (2012) 451–458

CHRONIC MORPHINE EXPOSURE AFFECTS CONTRAST RESPONSE FUNCTIONS OF V1 NEURONS IN CATS

T. SONG,[a] G. LI,[a] Z. LIANG,[c] Y. TANG,[a] Y. YANG,[a] G. LI,[a] J. XIA[a] AND Y. ZHOU[a,b]*

[a] *CAS Key Laboratory of Brain Function and Diseases, and School of Life Sciences, University of Science and Technology of China, Hefei 230027, PR China*

[b] *State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Science, Beijing 100101, PR China*

[c] *Department of Bio-medical Engineering, School of Life Sciences, Anhui Medical University, Hefei 230032, PR China*

Abstract—Opiates disrupt neural functions in many brain areas, including visual cortex. Previous studies have indicated substantial changes of many neuronal response properties induced by chronic morphine exposure in the visual information processing system. However, it remains unclear whether neuronal contrast coding is also affected. To investigate this issue, we measured the contrast response functions (CRFs) of V1 neurons in chronic morphine-treated and saline-treated cats by using extra-cellular single-unit recording techniques. Our results indicated significantly lower contrast sensitivity in morphine-treated cats than in saline-treated cats and V1 neurons in morphine-treated cats exhibited enhanced maximum visual responses, higher baseline responses and lower signal-to-noise ratios compared with saline-treated cats. These findings provide some neurobiological evidence for the morphine-mediated degenerations of the visual cortex, which could underlie the opiate-induced deficits in visual function. **© 2012 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: morphine, contrast sensitivity, contrast response function, primary visual cortex, cat.

INTRODUCTION

For the well-known analgesic effect but the physiological dependence (Koob and Le Moal, 1997), the use of opiates must be carefully limited. In spite of this, opiate abuse is still a severe social and medical problem in the world. On this account, more and more attention has been attracted on the opiate-mediated injury mechanisms in the central neural system. It has been indicated that the visual system is rich in opiate receptors (Wise and Herkenham, 1982; Lewis et al., 1983; Walker et al., 1988), suggesting that visual system is subject to opiate modulation. Indeed, a number of studies have shown many opiate-induced behavior changes, such as abnormal visual discrimination performance in rats (Grilly et al., 1980) and reduced visual sensitivity in humans (Rothenberg et al., 1979) and pigeons (Nielsen and Appel, 1983). Morphological studies in our lab also reveal that chronic morphine administration leads to the prominent structural modification in the primary visual cortex (Li et al., 2007c; Hu et al., 2008). Additionally, many visual response properties of the neurons in LGN and V1, such as response modulation (He et al., 2005b), orientation and direction selectivity (He et al., 2005a,c) and the visual response latency (Long et al., 2008), are found to be significantly affected by chronic morphine exposure. Taken together, these results indicate a substantial influence of opiates on the visual system.

Coding of contrast plays an important role in the visual information processing. Psychophysical studies indicate that human motion perception is contrast-dependent (Stone and Thompson, 1992; Edwards et al., 1996). It has also been suggested that variation of stimulus contrast can influence the neuronal tuning for other parameters, such as spatial frequency and speed (Sceniak et al., 2002; Alitto and Usrey, 2004). Up to now, few studies have focused on the effects of opiates on contrast response functions (CRFs) of the neurons in the visual cortex. In the present study, we used extracellular single-unit recording techniques to examine the effect of chronic morphine exposure on the contrast response functions of V1 neurons.

EXPERIMENTAL PROCEDURES

Animal preparation and drug exposure

The experiments were performed on six adult cats, which were divided into two groups: the morphine-treated cats (MCs, $n = 3$) and the saline-treated cats (SCs, $n = 3$). Cats were well examined ophthalmoscopically before the experiment and had no apparent optical problems or retinal problems that would impair visual functions. The methods of morphine administration we used were identical to previously described (Pu et al., 2002; He et al., 2005a). Morphine cats were given morphine HCl (10 mg/kg) by cervical region hypodermic twice per day at 9:00 and 21:00 for 10 days before electrophysiological experiments. Control animals were given

*Correspondence to: Y. Zhou, CAS Key Laboratory of Brain Function and Diseases, and School of Life Sciences, University of Science and Technology of China, Hefei 230027, PR China. Tel: +86-551-3601436; fax: +86-551-3601443.
E-mail address: zhouy@ustc.edu.cn (Y. Zhou).

Abbreviations: CRFs, contrast response functions; MCs, morphine-treated cats; SCs, saline-treated cats; SNR, signal-to-noise ratio.

0306-4522/12 $36.00 © 2012 IBRO. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuroscience.2012.09.042

saline instead of morphine the same way. During electrophysiological recording, morphine or saline was injected in the same way.

All experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Science and Technology of China, and were consistent with the Society for Neuroscience and National Institutes of Health guidelines for the humane use and care of animals. All efforts were made to reduce the numbers of animals to the smallest amount and minimize their suffering in the experiments.

Surgical operation and extra-cellular recording

On the 11th day of morphine administration, animals were prepared for extra-cellular single-unit recording. The methods were described elsewhere (Shou et al., 1996; Hua et al., 2006). Thus, only a short summary follows. Subjects were anesthetized prior to surgery with ketamine HCl (20 mg/kg), and then intravenous cannulas and tracheal intubation were inserted under sterile conditions. A long-acting anesthetic (1% lidocaine HCl) was applied to all pressure points and incisions of surgical entry. Cats were placed in a stereotaxic apparatus after surgery. Pupils were maximally dilated with atropine (1%), and nictitating membranes were retracted with neosynephrine (0.5%). Cats' eyes were protected from dryness and desiccation by wearing contact lenses. Animals were kept anesthetized and paralyzed with a mixture of urethane (20 mg/kg/h) and gallamine triethiodide (10 mg/kg/h) by intravenous injection throughout the experiments. To assess the level of anesthesia, heart rate (about 180–220 pulses/min) and EEG were monitored. Expired CO_2 was tested by a CO_2 monitor (MULTINEX, USA) and maintained at approximately 4%. Animals' body temperature was maintained at 38 °C with a heating pad. All cats were studied under similar stable, reliable recording. A craniotomy (diameter: 8 mm) in the midline, 4 mm posterior to the ear bars, was performed. And then the dura mater was removed. After a glass microelectrode was positioned, the small hole was covered with a 4% solution of agar in saline. For each unit, we chose the preferred eye and covered the other one by an opaque occluder. Action potentials of isolated cortical cells were recorded extracellularly with NaCl-in-glass microelectrodes having impedances of 2–4 MΩ.

Visual stimulation

Visual stimulus patterns were drifting sinusoidal gratings and all visual stimuli were displayed on a 17-inch Sony Multiscan G220 monitor (Sony Corporation, Tokyo, Japan) with a resolution of 1024 × 768 pixels and a frame rate of 100 Hz. The monitor was placed 57 cm away from animals' eyes. The mean luminance of the display was 45.2 cd/m^2 and the environment luminance on the cornea was approximately 0.1 lx. The program to generate the stimulus was written in MATLAB (Mathworks, Natick, USA), by using the extensions provided by the high-level Psychophysics Toolbox (Brainard, 1997) and the low-level Video Toolbox (Pelli, 1997). After isolating a single unit in V1 area, we carefully measured its receptive field properties, such as direction, orientation and spatial frequency turning curve. Then the drifting sinusoidal gratings with optimal parameters, a constant temporal frequency (2 Hz) and different contrasts ranging between 0.01 and 1.0 were presented in a pseudo-random order. Three trials for each contrast level were made to obtain CRF of each neuron. Stimulus contrast was defined as the subtraction between the maximum and minimum luminance divided by their sum. To avoid the response adaptation, blanks (4 s) of the mean luminance were interleaved between stimulus trials.

Date collection and analysis

The neuronal signals were amplified with a microelectrode amplifier (Nihon Kohden, Tokyo, Japan). Then, the amplified responses were fed into an audio monitor, and were digitized by an acquisition board (National Instruments, Austin, USA) controlled by IGOR software (WaveMetrics, Portland, USA). The original experiment data we obtained were stored in the computer for later analysis.

We used the following equation to analyze the data, which has been proved to well fit for the CRFs of cells of visual cortex in the cat and monkey (Albrecht and Hamilton, 1982; Kohn and Movshon, 2003): $R = R_{max} \times (\frac{C^n}{C^n + C_{50}^n}) + M$ where R is the neuronal response to contrast C, R_{max} is the neuronal maximum attainable response, C_{50} is the half-saturation contrast, n is the exponent determining the slope of the curve of CRF, and M represents the spontaneous activity. The smaller the values of C_{50}, the more contrast sensitive are the neurons. To explore the information processing ability, a cell's signal-to-noise ratio (SNR) was analyzed that was defined as the ratio of a cell's visual-evoked response to the optimal stimulus (contrast close to 1.0) and the cell's spontaneous activity. And for SNR analysis, all spontaneous activities below 1 spike/s were set for 1 spike/s (Schmolesky et al., 2000; Leventhal et al., 2003).

RESULTS

We recorded 80 V1 neurons from three MCs and 57 V1 neurons from three SCs. All neurons were recorded at the same range of depth from the surface of the brain to avoid laminar bias. In this study, there were no systematic differences in the effects of chronic morphine treatment on the complex and simple cells. Thus the data of both types of cells were considered together.

One typical cell from MCs and one from SCs are illustrated in Fig. 1. It is clear that these two cells exhibit different CRFs, with higher values of R_{max}, spontaneous activity, C_{50} and even exponent for the cell from MCs. Results of the analyses on these four parameters are described below in separate sessions.

Contrast sensitivity

Primary analyses (Fig. 2A) indicated that C_{50} of both groups were normally distributed (Kolmogorov–Smirnov Test, both Ps > 0.05). However, significant differences were found between these two distributions (two-sample Kolmogorov–Smirnov Test, $P < 0.001$). C_{50} in MCs varied with a wider range (from 0.10 to 0.77) than those in SCs (from 0.07 to 0.32). More than half of the cells (51.3%, 41 of 80) in MCs showed low contrast sensitivity ($C_{50} \geqslant 0.3$) while only 7.0% of the cells (4 of 57) in SCs exhibited similar response property. On the other hand, the percentage of the cells that were highly contrast sensitive ($C_{50} \leqslant 0.1$) is greater in SCs (8.8%, 5 of 57) than in MCs (2.5%, 2 of 80). These results suggest that the contrast sensitivity of the cells in MCs is lower than in SCs, which was further supported by subsequent statistical analyses (Tables 1 and 2). As a group, cells in MCs showed significantly (two independent sample t-test, $P < 0.001$) higher C_{50} (0.32 ± 0.02) than those in SCs (0.19 ± 0.01). These findings indicate a substantial decline in contrast sensitivity induced by chronic morphine exposure.

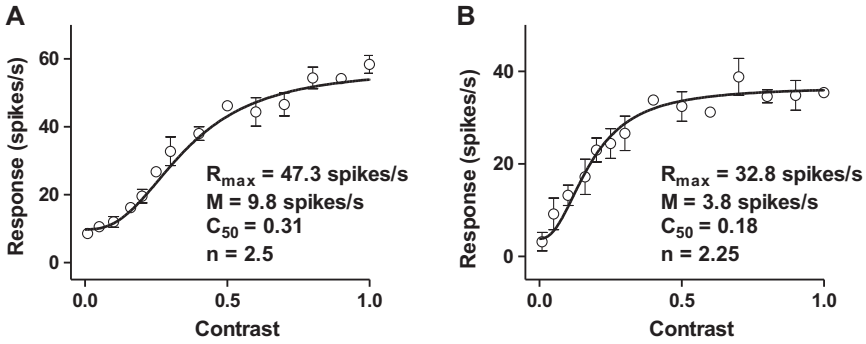

Fig. 1. Contrast response functions obtained from a typical neuron in MCs (A) and a typical neuron in SCs (B). Responses are to drifting sinusoidal gratings of randomly varied contrast from 0.05 to 1.0 at 14 levels. Each point represents the response to the stimulus with a given contrast. Neurons in MCs show increased maximum visual responses (R_{max}), spontaneous activities (M), half-saturation contrasts (C_{50}) but comparable exponents (n) when compared with neurons in SCs. Error bars indicate SEM.

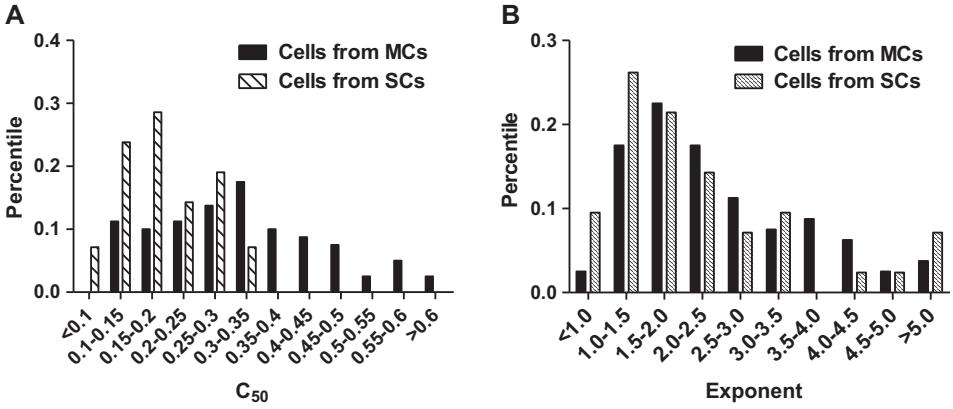

Fig. 2. Percentage of V1 neurons with different C_{50} (A) and exponent (n) values (B) in MCs and SCs. The total number of neurons is 80 for MCs and 57 for SCs, respectively. Neurons in MCs exhibit significantly ($P < 0.001$) larger C_{50} than those in MCs. In contrast, there is no significant difference ($P = 0.057$) in exponent values between two groups.

Table 1. Descriptive statistics of visual response properties of V1 neurons for each cat

Cat	N	C_{50}	n	R_{max}	M	SNR
SC1	17	0.19 ± 0.02	2.00 ± 0.35	33.7 ± 4.2	4.1 ± 0.7	10.0 ± 1.9
SC2	19	0.18 ± 0.02	2.46 ± 0.39	36.0 ± 3.3	4.3 ± 0.6	11.1 ± 2.8
SC3	21	0.21 ± 0.02	2.20 ± 0.41	37.4 ± 6.6	4.8 ± 0.9	10.2 ± 2.7
MC1	24	0.34 ± 0.03	2.62 ± 0.21	48.2 ± 4.6	8.8 ± 0.9	6.8 ± 0.8
MC2	26	0.31 ± 0.03	2.51 ± 0.24	49.8 ± 4.3	11.3 ± 2.0	5.6 ± 0.6
MC3	30	0.33 ± 0.03	2.90 ± 0.55	52.0 ± 3.9	12.3 ± 1.8	5.3 ± 0.5

Experimental animals were briefly named as SC1–3 (for saline-treated cats 1–3) and MC1–3 (for morphine-treated cats 1–3). Other data columns represent the number of cells (N), C_{50}, exponent (n), R_{max}, baseline response (M) and signal-to-noise ratio (SNR). Data are expressed as mean ± SEM.

Table 2. Descriptive statistics of visual response properties of V1 cells between MCs and SCs

Properties	Neurons in MCs (n = 80)	Neurons in SCs (n = 57)	Mann–Whitney U test
C_{50}	0.32 ± 0.02	0.19 ± 0.01	$P < 0.001$*
n	2.69 ± 0.23	2.25 ± 0.22	$P = 0.057$
R_{max} (spikes/s)	50.0 ± 2.4	33.5 ± 2.7	$P < 0.001$
M (spikes/s)	10.6 ± 0.8	4.4 ± 0.4	$P < 0.001$
SNR	6.0 ± 0.4	10.5 ± 1.5	$P < 0.001$

Two group comparisons of C_{50}, exponent (n), R_{max}, baseline response (M) and signal-to-noise ratio (SNR) were performed between MCs and SCs. Data are expressed as mean ± SEM. Since most of these properties do not exhibit normal distributions (Kolmogorov–Smirnov Test, most Ps < 0.05), Mann–Whitney U test is applied here.

* C_{50} is normally distributed (Kolmogorov–Smirnov Test, both Ps > 0.05) for two groups and the result of two independent sample t-test ($P < 0.001$) is also consistent with that of Mann–Whitney U test.

It is possible that differential effects of anesthesia on contrast response functions of V1 neurons in saline- and morphine-treated cats could influence our results. To test this possibility, we recorded the properties of individual neurons while varying anesthetic and paralytic levels in our experiment. One typical cell from MCs and one from SCs are illustrated in Fig. 3. We found that when we systematically changed anesthesia and paralytic levels, giving as much as four times the minimum level required to anesthetize or paralyze cat almost does not affect the degree of contrast sensitivity of V1 neurons. The results suggest that contrast response functions are barely dependent on the level of anesthesia.

The slope of CRFs

Exponents of the two groups were also analyzed (Fig. 2B) and they exhibited different distributions (Kolmogorov–Smirnov Test, $P = 0.006$ and 0.180 for MCs and SCs, respectively). Consistent with this result, a marginal difference (two-sample Kolmogorov–Smirnov Test, $P = 0.066$) was found between these two distributions. Indeed, the peak of the distribution for MCs is slightly rightward to that for SCs. Based on these findings, we further conduct Mann–Whitney U test to reveal the exact difference of the exponents between MCs and SCs. The results (Tables 1 and 2) suggested that the exponents were slightly ($P = 0.057$) larger in MCs (from 0.72 to 6.51, mean 2.69, median 2.22) than in SCs (from 0.68 to 6.79, mean 2.25, median 1.74).

Since the exponent characterizes the steepness of CRF, with larger values indicating steeper slopes, and steeper slopes may help neurons maintain high contrast sensitivity (Sclar et al., 1990; Yang et al., 2008), it is surprising to see slightly larger exponents in MCs than in SCs. However, as the slope characterizes the relation

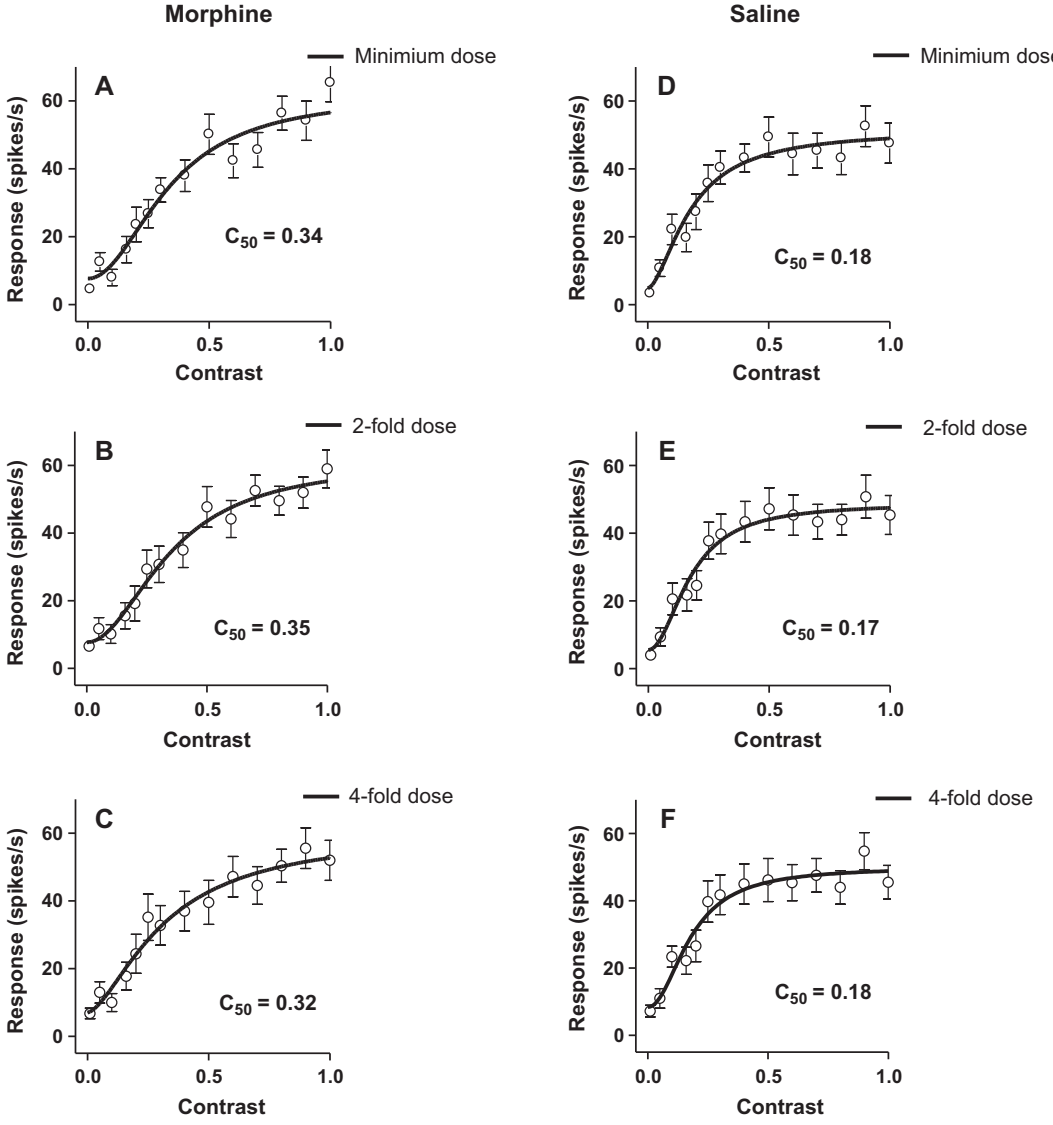

Fig. 3. Examples of effects of anesthesia on the contrast response functions of V1 neurons. Contrast response functions obtained from a typical neuron in MCs with different anesthesia levels (A–C) and a typical neuron in SCs with different anesthesia levels (D–F). Responses are to drifting sinusoidal gratings of randomly varied contrast from 0.05 to 1.0 at 14 levels. Each point represents the response to the stimulus with a given contrast. Neurons in MCs exhibit larger C_{50} than those in MCs and anesthesia does not affect the degree of contrast sensitivity of V1 neurons.

between the contrasts and visually evoked responses of the cells, the larger exponents of the cells in MCs may be attributed to their increased peak responses and spontaneous activities (described in the following session). It is clear (see in Tables 1 and 2) that the contrast ranges in two groups are identical, while the response range in MCs (from mean spontaneous activity, 10.6 spikes/s, to mean maximum visual-evoked responses, 50.0 spikes/s) is greater than that in SCs (from 4.4 spikes/s to 33.5 spikes/s). The former is about 1.4 times larger than the latter. Generally speaking, this difference in visually evoked responses will lead to a disparity of the exponent values with a similar scale. On the other hand, it seems that the exponents in MCs (mean 2.69) are only about 1.2 times larger than those in SCs (mean 2.25). These findings suggest that the exponents may not be higher in MCs than in SCs after excluding the influence of the response range.

To further investigate this issue, neuronal responses to stimuli with different contrasts were normalized to its maximum response and then CRF was re-estimated for each cell as well as average normalized response of each group. As expected, the results (Fig. 4 and Table 3) showed that the exponents were slightly larger in SCs (from 0.58 to 6.63, mean 2.93, median 1.90) than in MCs (from 0.89 to 6.48, mean 2.44, median 1.87) at this time, different from the findings before normalization.

Maximum visual response, baseline response and signal-to-noise ratio

We also analyzed the maximum visual responses (R_{max}), baseline responses (M) and the signal-to-noise ratios of all recorded neurons in MCs and SCs, with the results shown in Tables 1, 2 and Fig. 5. In line with the previous findings (He et al., 2005a), we found that cells in MCs exhibited significantly higher maximum visual responses (50.0 ± 2.4 vs. 33.5 ± 2.7, Mann–Whitney U test, $P < 0.001$) and baseline responses (10.6 ± 0.8 vs. 4.4 ± 0.4, Mann–Whitney U test, $P < 0.001$) than those in SCs. It is noteworthy that the percent difference of the baseline responses (58%) between MCs and SCs are larger than that of the maximum visual response (33%). SNR of neurons in MCs (6.0 ± 0.4) were also much smaller (Mann–Whitney U test, $P < 0.001$) than those in SCs (10.5 ± 1.5), suggesting weaker ability in extracting and conveying signals from the noisy backgrounds for the former.

DISCUSSION

In this study, we examined the effects of chronic morphine exposure on the contrast response functions of V1 neurons in cats. Our results indicated higher C_{50}, maximum and baseline responses in MCs than those in SCs. Additionally, signal-to-noise ratios were found to be lower in MCs, consistent with the previous study (He et al., 2005a). These findings support the idea that the neural functions are substantially influenced by chronic morphine exposure in the visual system (He et al., 2005a,b,c; Li et al., 2007a; Hu et al., 2008; Long et al., 2008).

Previous studies have suggested that decreased intro-cellular inhibition may contribute to the increase of spontaneous activity and maximum response as well as the decline in signal-to-noise ratio. It is also suggested that the efficacy of cortical inhibitory functions declines with chronic morphine administration (Ticku and Huffman, 1980; Schoffelmeer et al., 2001). Our results that V1 cells in MCs showed increased spontaneous, visually driven activity and decreased signal-to-noise ratios may be particularly consistent with the hypothesis. In some brain regions, systemic morphine administration could reduce GABA release (Renno et al., 1992). Our lab has also found that GABAergic system is affected by chronic morphine exposure in the visual cortex (Li et al., 2007b). Visual cortex neurons that received weak inhibition can significantly improve their function response characteristic by GABA administration (Leventhal et al., 2003; Li et al., 2008) and application of GABAa receptor antagonists resulted in increased stimulus-driven and spontaneous activity (Thiele et al., 2004). Thus, the decreased receptive field characteristic of V1 neurons in MCs, including increased spontaneous activity and decreased signal-to-noise ratios, may be correlated with the dysfunction of GABAergic system.

Contrast encoding is an important response property of the neurons in the visual pathway and coding of image contrast has served as a paradigm for studying how visual information is encoded into the responses of

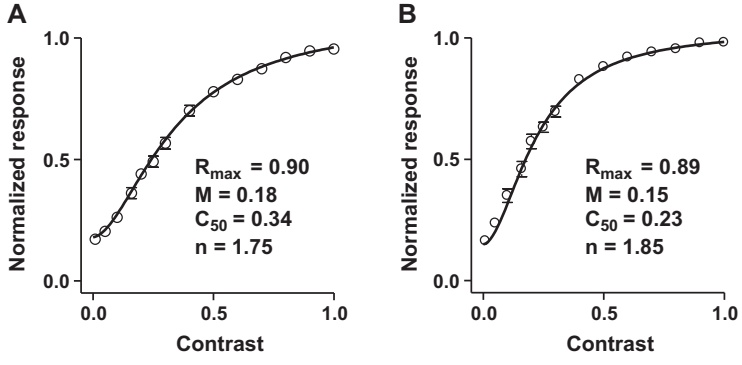

Fig. 4. Contrast response function for average normalized response of MCs (A) and SCs (B). It is clear that the C_{50} is higher in MCs while the exponent is higher in SCs.

Table 3. Descriptive statistics of visual response properties of V1 cells between MCs and SCs after normalization

Properties	Neurons in MCs (n = 80)	Neurons in SCs (n = 57)	Statistical comparison
C_{50}	0.35 ± 0.02	0.22 ± 0.01	$P < 0.001$*
n	2.44 ± 0.25	2.93 ± 0.39	$P = 0.730$#

Two group comparisons of C_{50} and exponent (n) were performed between MCs and SCs. Data are expressed as mean ± SEM.

* Two independent sample t-test.

Mann–Whitney U test.

the visual cells. Our results that significant changes exist in contrast response function between MCs and SCs provide the first evidence of the influence of chronic morphine exposure on neuronal contrast encoding. Chronic morphine exposure induces adaptation of the neural system to opiates. It is well known that opiate abuse can change both inhibitory and excitatory neurotransmission in many brain areas (Martin et al., 1999; Laviolette et al., 2004). So far most studies on the neural mechanisms modulating contrast response functions of neurons in the visual cortex are focused on inhibitory neurotransmission (Thiele et al., 2004). Several papers have suggested that contrast normalization of cortical neurons is mediated by intracortical suppression (Carandini et al., 1997; Britten and Heuer, 1999). Specially, GABAergic mechanisms are thought to mediate contrast normalization in visual cortex (Thiele et al., 2004). In addition, some studies have shown that dopaminergic system is closely linked to morphine addiction (Koob, 1992; Robbins and Everitt, 1999). Domenici et al. have found that dopaminergic drugs can improve human visual contrast sensitivity (Domenici et al., 1985). Though research on opiate abuse suggests that the decline of inhibitory neurotransmission actually happens in many brain regions, there is also a study showing that chronic opiate exposure affects excitatory neurotransmission such as glutamatergic (Martin et al., 1999). Additionally, our previous study has shown that chronic morphine exposure causes morphological changes in pyramidal cells of V1 (Li et al., 2007c; Hu et al., 2008) and impacts the LGN (Long et al., 2008), suggesting that excitatory inputs to V1 and excitatory V1 neurons themselves are directly influenced by morphine. It is tempting to speculate that despite the effect of intracortical suppression, the decreased excitatory input from LGN and/or other cortical cells may have a role in decreasing the contrast sensitivity of V1 neurons. In summary, our results, together with our previous study and others, suggest that a combined change of excitatory and inhibitory neurotransmission might contribute to the decreased contrast sensitivity of V1 neurons to visual stimuli in morphine-treated cats. However, more studies are required to ascertain it.

Previous studies have shown that single exposure to morphine is enough to persistently reduce nonvesicular GABA release and may be sufficient to induce long-lasting behavioral hyperresponsiveness and neurochemical sensitization in the nucleus accumbens (Ticku and Huffman, 1980; Schoffelmeer et al., 2001). It is tempting to speculate that acute morphine administration may also affect the contrast response functions of V1 neurons in cats. However, our previous data (He et al., 2005b) have shown that chronic morphine exposure results in the degradation of response modulation of V1 neurons while acute morphine injection causes no change of response modulation of visual cortical neurons and response modulation of neurons is also affected by GABAergic system. So the effects of acute morphine administration on CRF need further investigation.

Our main results showed that the contrast sensitivity of the cells in MCs is lower than in SCs. Contrast is thought to affect the percept of speed and spatial frequency tuning. Previous studies have shown that most V1 cells in macaques shifted their speed tuning to slower speeds for lower contrast stimuli (Livingstone and Conway, 2007). Reduction of stimulus contrast causes expansion of spatial summation at low contrast (Sceniak et al., 2002). So, we hypothesize that chronic morphine exposure may affect speed and spatial frequency tuning. Further experiments are needed to ascertain it.

It is concerned that perhaps the effects of anesthesia and morphine on neuronal response function could influence our results. In our experiments, ketamine was only used before electrophysiological recording to keep

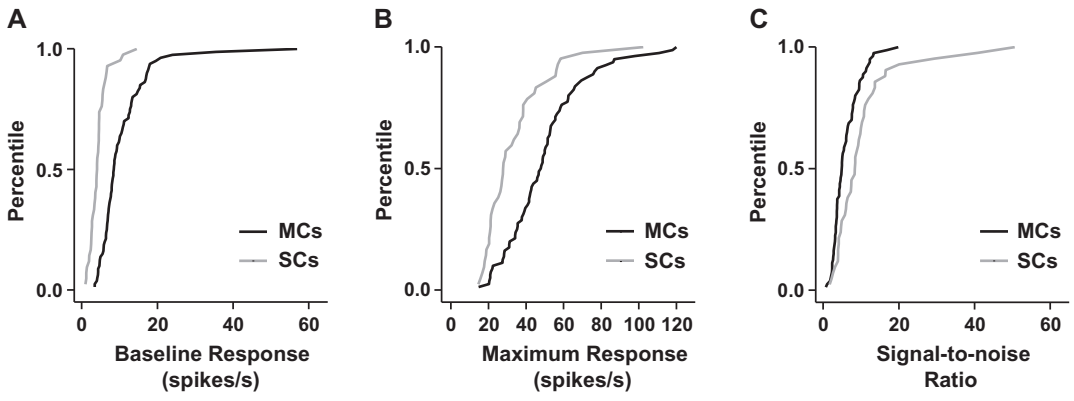

Fig. 5. Cumulative distributions of the baseline responses (A), maximum responses (B) and the signal-to-noise ratio (C) of V1 cortical cells in MCs and SCs. Cells in MCs exhibited higher baseline responses, maximum responses and lower signal-to-noise ratios than those in SCs.

anesthesia during surgery. And it was suited for electrophysiological research in visual information processing (Leopold et al., 2002), due to no visible suppression to the cortical neuronal activities (Kalkman et al., 1994). Urethane was used to maintain anesthesia during the whole electrophysiological recordings, because of its minimal effects on cardiovascular and respiratory systems and maintenance of spinal reflexes (Hara and Harris, 2002). It was considered well suitable for physiopharmacological and pharmacological investigations, especially for the studies of GABAergic system and its modulation by drugs (Maggi and Meli, 1986). Nevertheless, it is not easy to exclude a combined effect of morphine and urethane in our experiments. So we recorded the properties of individual neurons while varying anesthetic and paralytic levels in our experiment, and we found that when we systematically changed anesthesia and paralytic levels, giving as much as four times the minimum level required to anesthetize or paralyze cat does not alter the degree of contrast sensitivity of V1 neurons significantly. In fact, as an anesthetic, urethane has been widely used in animal studies to explore the effect of chronic morphine exposure on neuronal activity of different brain regions including visual cortex (Rayner et al., 1988; Afarinesh et al., 2008). Therefore, we conclude that the problem with anesthesia is not a concern and it cannot influence our results.

Exploring the effect of opiate abuse on contrast response function of visual cortex, based on the information of structure and function of visual system, would be beneficial to the understanding of the influence and underlying mechanisms of drug abuse. Also, it can help us to know more about the role of opiate receptors in the visual system. Our findings provide new neurobiological evidence of the functional degeneration in the visual system induced by chronic morphine exposure. It is suggested that these changes in neuronal response properties may underlie the opiate-induced visual disruptions reported previously.

Acknowledgments—This investigation was supported by grants from the National Natural Science Foundation of China (30470561, 30070257) and National Basic Research Program of China (2009CB941303). The NSFC and NBRP had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

REFERENCES

Afarinesh MR, Sheibani V, Arabzadeh S, Shamsizadeh A (2008) Effect of chronic morphine exposure on response properties of rat barrel cortex neurons. Addict Biol 13:31–39.

Albrecht DG, Hamilton DB (1982) Striate cortex of monkey and cat: contrast response function. J Neurophysiol 48:217–237.

Alitto HJ, Usrey WM (2004) Influence of contrast on orientation and temporal frequency tuning in ferret primary visual cortex. J Neurophysiol 91:2797–2808.

Brainard DH (1997) The psychophysics toolbox. Spat Vis 10:433–436.

Britten KH, Heuer HW (1999) Spatial summation in the receptive fields of MT neurons. J Neurosci 19:5074–5084.

Carandini M, Heeger DJ, Movshon JA (1997) Linearity and normalization in simple cells of the macaque primary visual cortex. J Neurosci 17:8621–8644.

Domenici L, Trimarchi C, Piccolino M, Fiorentini A, Maffei L (1985) Dopaminergic drugs improve human visual contrast sensitivity. Hum Neurobiol 4:195–197.

Edwards M, Badcock DR, Nishida S (1996) Contrast sensitivity of the motion system. Vision Res 36:2411–2421.

Grilly DM, Genovese RF, Nowak MJ (1980) Effects of morphine, d-amphetamine, and pentobarbital on shock and light discrimination performance in rats. Psychopharmacology (Berl) 70:213–217.

Hara K, Harris RA (2002) The anesthetic mechanism of urethane: the effects on neurotransmitter-gated ion channels. Anesth Analg 94:313–318.

He L, Li X, Hua T, Bao P, Ma R, Zhou Y (2005a) Chronic morphine exposure affects the visual response properties of V1 neurons in cat. Brain Res 1060:81–88.

He L, Li X, Hua T, Bao P, Zhou Y (2005b) Degradation of response modulation of visual cortical cells in cats with chronic exposure to morphine. Neurosci Lett 384:168–171.

He LH, Li GX, Li XR, Zhou YF (2005c) Chronic morphine exposure induces degradation of receptive field properties of LGN cells in cats. Acta Pharmacol Sin 26:1034–1038.

Hu F, Li G, Liang Z, Yang Y, Zhou Y (2008) The morphological changes of pyramidal and spiny stellate cells in the primary visual cortex of chronic morphine treated cats. Brain Res Bull 77:77–83.

Hua T, Li X, He L, Zhou Y, Wang Y, Leventhal AG (2006) Functional degradation of visual cortical cells in old cats. Neurobiol Aging 27:155–162.

Kalkman CJ, Drummond JC, Patel PM, Sano T, Chesnut RM (1994) Effects of droperidol, pentobarbital, and ketamine on myogenic transcranial magnetic motor-evoked responses in humans. Neurosurgery 35:1066–1071.

Kohn A, Movshon JA (2003) Neuronal adaptation to visual motion in area MT of the macaque. Neuron 39:681–691.

Koob GF (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 13:177–184.

Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. Science 278:52–58.

Laviolette SR, Gallegos RA, Henriksen SJ, van der Kooy D (2004) Opiate state controls bi-directional reward signaling via GABAA receptors in the ventral tegmental area. Nat Neurosci 7:160–169.

Leopold DA, Plettenberg HK, Logothetis NK (2002) Visual processing in the ketamine-anesthetized monkey. Optokinetic and blood oxygenation level-dependent responses. Exp Brain Res 143: 359–372.

Leventhal AG, Wang Y, Pu M, Zhou Y, Ma Y (2003) GABA and its agonists improved visual cortical function in senescent monkeys. Science 300:812–815.

Lewis ME, Pert A, Pert CB, Herkenham M (1983) Opiate receptor localization in rat cerebral cortex. J Comp Neurol 216:339–358.

Li G, Yang Y, Liang Z, Xia J, Zhou Y (2008) GABA-mediated inhibition correlates with orientation selectivity in primary visual cortex of cat. Neuroscience 155:914–922.

Li Y, He L, Chen Q, Zhou Y (2007a) Changes of micro-opioid receptors and GABA in visual cortex of chronic morphine treated rats. Neurosci Lett 428:11–16.

Li Y, Wang H, Niu L, Zhou Y (2007b) Chronic morphine exposure alters the dendritic morphology of pyramidal neurons in visual cortex of rats. Neurosci Lett 418:227–231.

Livingstone MS, Conway BR (2007) Contrast affects speed tuning, space-time slant, and receptive-field organization of simple cells in macaque V1. J Neurophysiol 97:849–857.

Long Z, Liang Z, He L, Zhou Y (2008) Chronic morphine exposure affects visual response latency of the lateral geniculate nucleus in cats. Clin Exp Pharmacol Physiol 35:1222–1226.

Maggi CA, Meli A (1986) Suitability of urethane anesthesia for physiopharmacological investigations in various systems: Part 1. General considerations. Experientia 42:109–114.

Martin G, Ahmed SH, Blank T, Spiess J, Koob GF, Siggins GR (1999) Chronic morphine treatment alters NMDA receptor-mediated

synaptic transmission in the nucleus accumbens. J Neurosci 19:9081–9089.
Nielsen EB, Appel JB (1983) The effects of drugs on the discrimination of color following a variable delay period: a signal detection analysis. Psychopharmacology (Berl) 80:24–28.
Pelli DG (1997) The VideoToolbox software for visual psychophysics: transforming numbers into movies. Spat Vis 10:437–442.
Pu L, Bao GB, Xu NJ, Ma L, Pei G (2002) Hippocampal long-term potentiation is reduced by chronic opiate treatment and can be restored by re-exposure to opiates. J Neurosci 22:1914–1921.
Rayner VC, Robinson IC, Russell JA (1988) Chronic intracerebroventricular morphine and lactation in rats: dependence and tolerance in relation to oxytocin neurons. J Physiol 396:319–347.
Renno WM, Mullett MA, Beitz AJ (1992) Systemic morphine reduces GABA release in the lateral but not the medial portion of the midbrain periaqueductal gray of the rat. Brain Res 594:221–232.
Robbins TW, Everitt BJ (1999) Drug addiction: bad habits add up. Nature 398:567–570.
Rothenberg S, Peck EA, Schottenfeld S, Betley GE, Altman JL (1979) Methadone depression of visual signal detection performance. Pharmacol Biochem Behav 11:521–527.
Sceniak MP, Hawken MJ, Shapley R (2002) Contrast-dependent changes in spatial frequency tuning of macaque V1 neurons: effects of a changing receptive field size. J Neurophysiol 88:1363–1373.
Schmolesky MT, Wang Y, Pu M, Leventhal AG (2000) Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. Nat Neurosci 3:384–390.
Schoffelmeer AN, Wardeh G, Vanderschuren LJ (2001) Morphine acutely and persistently attenuates nonvesicular GABA release in rat nucleus accumbens. Synapse 42:87–94.
Sclar G, Maunsell JH, Lennie P (1990) Coding of image contrast in central visual pathways of the macaque monkey. Vision Res 30:1–10.
Shou T, Li X, Zhou Y, Hu B (1996) Adaptation of visually evoked responses of relay cells in the dorsal lateral geniculate nucleus of the cat following prolonged exposure to drifting gratings. Vis Neurosci 13:605–613.
Stone LS, Thompson P (1992) Human speed perception is contrast dependent. Vision Res 32:1535–1549.
Thiele A, Distler C, Korbmacher H, Hoffmann KP (2004) Contribution of inhibitory mechanisms to direction selectivity and response normalization in macaque middle temporal area. Proc Natl Acad Sci USA 101:9810–9815.
Ticku MK, Huffman RD (1980) The effects of acute and chronic morphine administration on GABA receptor binding. Eur J Pharmacol 68:97–106.
Walker JM, Bowen WD, Thompson LA, Frascella J, Lehmkuhle S, Hughes HC (1988) Distribution of opiate receptors within visual structures of the cat brain. Exp Brain Res 73:523–532.
Wise SP, Herkenham M (1982) Opiate receptor distribution in the cerebral cortex of the Rhesus monkey. Science 218:387–389.
Yang Y, Liang Z, Li G, Wang Y, Zhou Y, Leventhal AG (2008) Aging affects contrast response functions and adaptation of middle temporal visual area neurons in rhesus monkeys. Neuroscience 156:748–757.

(Accepted 19 September 2012)
(Available online 25 September 2012)