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Degradation of response modulation of visual cortical cells in cats with chronic exposure to morphine

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Abstract

The primary visual cortex (V1) plays an important role in vision and visual perception. Studies in many brain regions demonstrate that opiate abuse can change excitatory and inhibitory neurotransmission. To investigate the effect of chronic morphine exposure on the response modulation of V1 simple and complex neurons, we carried out in vivo extracellular recordings in V1 of morphine- and saline-treated (control) cats. Response modulation was quantified as the ratio of first Fourier components (F1) to the mean response (F0). Compared with saline-treated cats, V1 neurons in morphine-treated cats exhibited weaker response modulation and a longer time course of response. The decrease of response modulation was caused by an increase of F0. Further, morphine re-exposure significantly improved the response properties of V1 neurons in morphine-treated cats. These results suggest that chronic morphine treatment leads to a significant degradation of response modulation of V1 neurons and a morphine dependence of primary visual cortical function.

Keywords: Simple cell; Complex cell; Response modulation; Visual cortex; Morphine; Cat

The primary visual cortex (V1) is not only a relay station between the lateral geniculate nucleus (LGN) of the thalamus and the other cortical regions, but also transforms input of LGN and plays an important role in vision and visual perception [1].

Based on differences of receptive field properties of visual cortical cells, Hubel and Wiesel described two basic types of neurons in the visual cortex: simple cells and complex cells [8]. After reviewing the results of many studies, Skottun et al. provided a simple and objective method to classify simple and complex cells based on response modulation. When using sinusoidal grating as stimuli, the ratio of first Fourier components (F1) to the mean components (F0) of response to an optimal stimulus provides a measure of the relative modulation of the response in a visual cortical cell [21]. When the ratio is above 1, the cell is classified as a simple cell. If the ratio is below 1, the cell is classified as a complex cell [21].

It has been proposed that inhibition contributes to the generation of simple and complex cell properties, and that blockade of inhibition widens ON and OFF subfields of simple cells, and the increased overlap between subfields might make their responses similar to those of complex cells [15,20]. Recent studies have suggested that chronic opiate exposure could change inhibitory neurotransmission [5,11] as well as excitatory neurotransmission [14,16] in different brain areas. Although opiate receptors express extensively in the visual system of cats [23], macaques [24] and rats [12], it is unknown whether and how chronic opiate exposure would affect response modulation in V1 cell of cat. In this study, we compare the response modulation of primary visual cortex cells in chronic morphine- and saline-treated cats (control), and studied the effect of morphine re-exposure on response modulation.

The data were obtained from 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

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the Care and Use of Laboratory Animals. According to the protocols of morphine treatment on cat [7] and rat [16,22], animals were treated by cervical subcutaneous injection of morphine HCl (10 mg/kg) twice per day at 9:00 a.m. and 9:00 p.m. for 10 days. Control cats were treated similarly with saline instead of morphine.

All cats were examined ophthalmoscopically before the electrophysiological experiment to ascertain that they had no optical problems or obvious retinal abnormality that would impair visual function. The cells studied had receptive fields located within 8° from the area centralis.

On the 11th day of morphine administration, the animal was prepared For extracellular single-unit recording as described previously [19,25]. Briefly, cats were initially anesthetized with ketamine HCl (20 mg/kg). Intravenous and tracheal cannulae were inserted. Lidocaine (1%) was applied to all incisions of surgical entry. Animals were kept anesthetized with urethane (20 mg/h/kg) and completely paralyzed with gallamine triethiodide (10 mg/h/kg) throughout the experiments. Electrocardiogram and electroencephalogram were continuously monitored. Expired CO_2 was maintained at 4%, and body temperature was maintained at 38 °C. Eyes were protected with contact lenses and focused at a distance of 57 cm. Receptive fields were first hand-plotted using flashing and moving bars and classified as simple or complex cells [8,21]. Computer-controlled visual stimuli consisting of drifting sinusoidal gratings were presented on a CRT monitor (1024 × 768, 85 Hz). We selected the optimal stimulus size, temporal frequency, spatial frequency and drifting direction for each cell. Each stimulus was presented monocularly to the dominant eye. The contrast for each stimulus was set at 80%. The mean luminance of the display was 19 cd/m^2, and the environmental luminance on the cornea was 0.1 lux. A typical recording lasted for 3 days. And during recording, morphine or saline was injected in the same way as described above.

As Skottun et al. [21], we calculated F1/F0 ratio of each V1 neuron. Approximately half of V1 neurons (46.7%; 98/210) had a high F1/F0 ratio (>1) in saline-treated cats (Fig. 1A). In contrast, only a small proportion of V1 neurons (17.4%; 38/218) had a high F1/F0 ratio (>1) in morphine-treated cats (Fig. 1B). The mean F1/F0 ratio showed individual variability in both morphine-treated and saline-treated cats. An analysis comparing the average F1/F0 ratio between the two groups showed that the average F1/F0 ratio of V1 cells was significantly lower for morphine-treated cats (0.66 ± 0.41) than for saline-treated cats (1.03 ± 0.44; *t* test, $p < 0.0001$). These and analogous data are described as mean ± standard deviation, unless noted otherwise. Moreover, we analyzed in detail the time course of neuronal responses using the ratio of PSTH area to its peak value as an index. In order to reduce skewing of the data and provide a more conservative estimation, cells with mean response (F0) less than 8 spikes/s were excluded from this analysis, and the bin of PSTHs was set at 4 ms. The number of cells analyzed was 201 for morphine-treated cats and 186 for saline-treated cats. The average time course of response in morphine-treated cats (78.6 ± 33.4 ms) is significantly longer than that in saline-treated cats (58.8 ± 30.4 ms; *t* test, $p < 0.0001$). This suggests that chronic morphine exposure leads to the general degradation of response modulation of V1 neurons.

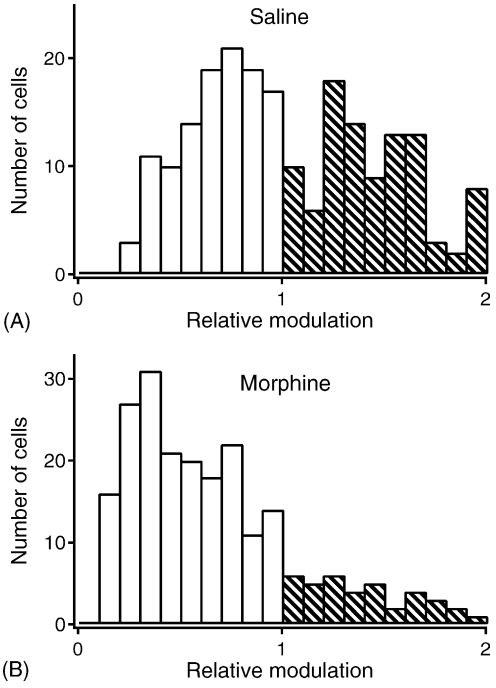

Fig. 1. Distribution of neuronal relative modulation. Average F1/F0 ratio of neurons between the two groups is significantly different (*t* test, $p < 0.0001$). Approximately half of V1 neurons (45.7%) have high F1/F0 ratios (>1) in saline-treated cats (A). Most of V1 cells (82.6%) have low F1/F0 ratios (<1) in morphine-treated cats (B).

To explore whether the decreased response modulation in morphine-treated cats resulted from an increased F0 value or from a decreased F1 value, or both, the F1 and F0 value of two groups were compared separately. The average F1 value showed no difference between two groups (21.2 ± 13.8 spikes/s versus 21.4 ± 15.9 spikes/s; *t* test, $p = 0.87$) (Fig. 2A). The average F0 value of V1 cells in morphine-treated cats (39.8 ± 24.4 spikes/s) was significantly larger than in saline-treated cats (23.7 ± 17.6 spikes/s; *t* test, $p < 0.0001$) (Fig. 2B). Therefore, the decrease of F1/F0 ratio should be attributed to the increased F0 value.

We examined the response modulation of V1 cells before and after morphine re-exposure. After 10 min of morphine re-exposure, we recorded the responses of 14 cells in morphine-treated cats again. Fig. 3A illustrates the PSTHs of a cell before and after morphine re-exposure. The morphine re-exposure changed the response of the cell to a narrower temporal range, from 51.1 to 44.9 ms. Compared to before morphine re-exposure, most cells (12/14) showed a shorter time course after morphine re-exposure (paired *t* test, $p < 0.05$). Fig. 3B illustrates that most cells (11/14) have a higher F1/F0 ratio after morphine re-exposure. A paired *t* test showed that the response modulation of neurons after morphine re-exposure improved significantly when

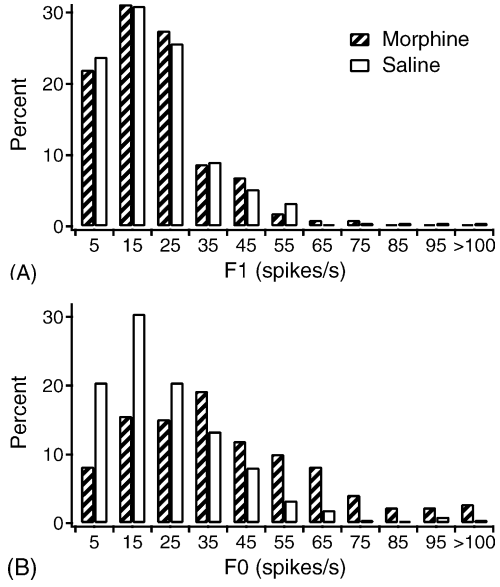

Fig. 2. Distribution of F1 and F0 value in the two groups. The two groups show similar distributions of F1 value (A), and average F1 value of neurons is not significantly different between the two groups (*t* test, $p = 0.87$). However, the distribution of F0 value shows differences between the two groups (B), and average F0 value of neurons in morphine-treated cats is larger than in saline-treated cats (*t* test, $p < 0.0001$).

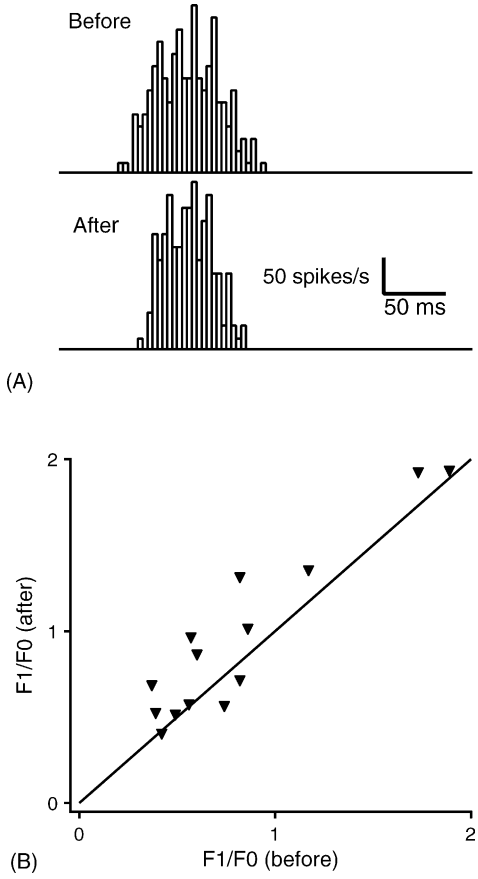

Fig. 3. Effect of morphine re-exposure on response modulation. (A) shows the PSTHs of a neuron before and after morphine re-exposure. The time course of this cell is shortened from 51.1 to 44.9 ms after morphine re-exposure. (B) shows that most cells (11/14) show increased F1/F0 ratio after morphine re-exposure (paired *t* test, $p < 0.05$), indicating that morphine re-exposure improved the response modulation of neurons of morphine-treated cats.

compared with before re-exposure ($p < 0.05$). Moreover, the response modulation of V1 neurons ($n = 3$) in saline-treated cats did not show significant increase or decrease after acute administration of morphine (paired *t* test, $p = 0.64$). These results suggest that chronic morphine exposure resulted in the morphine dependence of primary visual cortical function in morphine-treated cats.

In this study, we demonstrated the first evidence that chronic morphine exposure resulted in degradation of response modulation of visual cortical neurons, and morphine re-exposure could partly recover the decreased response modulation of V1 neurons in morphine-treated cats. It is possible that chronic morphine exposure led to an increased sample of complex cells. However, morphine re-exposure significantly improved the response modulation of V1 neurons in morphine-treated cats, and there was no change of response modulation in saline-treated cats following acute morphine injection. Therefore, the degradation of response modulation of V1 neurons is unlikely due to sampling difference across conditions.

In the absence of GABAergic inhibition, the spatial segregation of receptive fields of simple cells is lost, so that their responses are similar to those of complex cells [15,20]. Systemic morphine exposure could reduce GABA release [17], although increases of GABA release by chronic morphine have been reported as well [2,10]. The results presented here suggest that chronic morphine exposure leads to the decrease of response modulation of visual cortical cells. This suggests an increased overlap of ON and OFF subfields of V1 neurons in morphine-treated cats. This was similar to the observation of Pernberg et al., that blockage of GABAergic inhibition resulted in the greater overlap of ON and OFF subfields [15]. However, Rivadulla et al. reported the negative result that bicuculline (a $GABA_A$ receptor antagonist) injection did not change the modulation of simple or complex cells [18]. The discrepancy between Pernberg et al. and Rivadulla et al. may be due to a small sample of cells in both studies (Pernberg et al.: 3 of 6 simple cells for subfield expansion; Rivadulla et al.: 3 simple cells and 3 complex cells). Furthermore, distinct classes of GABAergic synapses target restricted subcellular domains of principal neurons, thereby differentially regulating the signal input, integration and output [4]. The subcellular restriction of GABAergic synapses may represent a more general mechanism to regulate spatial and temporal signaling both within and among principal neurons in sensory cortex [4].

On the other hand, chronic opiate exposure results in the change of glutamatergic neurotransmission as well [14,16]. Rivadulla et al. also reported that blockage of AMPA receptors increased the response modulation of complex cells even when inhibition was removed [18]. Although our results did not definitely show that modulation of complex cells was

influenced by chronic morphine exposure, the improvement of the cells with a low F1/F0 ratio after morphine re-exposure indicate that complex cells may also suffer the general degeneration of response modulation in morphine-treated cats. The up-regulation of GluR-A subunit, a subunit of AMPA-type glutamate receptors, had been observed in the brains of animals addicted to morphine and other drugs of abuse [6], which may represent some compensatory action for morphine effect and indicate that the response modulation of complex cells may change following chronic morphine exposure. Moreover, drug-induced changes of GluR-A subunit in various brain regions have been observed at both protein and mRNA levels [3,9,13]. However, no evidence shows that action of AMPA receptor is relevant to the response modulation of simple cells.

In summary, our results, together with that of others suggests that a combined change of excitatory and inhibitory neurotransmission contributes to the degradation of response modulation of V1 neurons in morphine-treated cats, and that complex and simple cells may undergo quite different processes of degradation. The effect of GABAergic and glutamatergic system on the response modulation of neurons is quite complex, and much remains to be studied about their role in the response modulation of visual cortical neurons. The mechanism about the response modulation as well as its morphine-derived degradation needs to be investigated further.

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