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RESEARCH ARTICLE

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Effects of neonatal C-fiber depletion on the integration of paired-whisker inputs in rat barrel cortex

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Abstract In the present study we used computer-controlled mechanical displacement of paired whiskers in normal and C-fiber-depleted rats to quantitatively examine the role of C-fibers in the receptive field properties of barrel cortical cells. In rodents when adjacent whiskers are stimulated prior to the main whisker responses to the main whisker are inhibited, the degree of inhibition being a function of the inter-deflection intervals. The adjacent-whisker-evoked inhibition of barrel cells in normal and C-fiber-depleted rats using neonatal capsaicin treatment were examined by stimulation of the adjacent whisker zero, 10, 20, 30, 50 and 100 ms prior to the main whisker deflection. C-fiber depletion reduced the suppressive effect of paired whisker stimulation at all of the tested inter-stimulus intervals without changing response latencies. The main effect was observed during the later phase of response (about 13–17 ms from stimulus onset) and not during the initial responses (7–12 ms). These results suggest that the inhibitory receptive field properties of low-threshold mechanical somatosensory cells are influenced by C-fibers.

Keywords Barrel cortex · Rat · Object recognition · Capsaicin

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Introduction

Layer IV of the rodent somatosensory (SmI) cortex consists of anatomically distinct clusters of cells, which are called barrels (Woolsey and Van der Loos 1970). Barrel cells respond to whiskers on the contralateral face (Welker 1971) and receive converging thalamocortical inputs from multiple whiskers (Moore and Nelson 1998; Zhu and Connors 1999). Deflection of the main whisker (MW) evokes higher discharge rates with lower response latencies than adjacent whiskers (AW) (Armstrong-James and Fox 1987; Welker et al. 1993). When AW are stimulated prior to the MW the response to the MW is inhibited, the degree of inhibition being a function of the inter-deflection interval (Simons 1985; Simons and Carvell 1989). It has been suggested that this surround inhibition is mainly cortical and that it is mediated through layer IV local circuitries (Brumberg et al. 1996; Simons and Carvell 1989). Alternatively, it has been suggested that the barrel cells' receptive fields are shaped by horizontal connections between multiple neighboring barrels (Armstrong-James et al. 1991; Fox 1994).

It has been shown that the receptive field properties of low-threshold mechanical somatosensory cells are influenced by C-fibers (Calford and Tweedale 1991; Katz et al. 1999; Kwan et al. 1996; Nussbaumer and Wall 1985; Wall et al. 1982). Capsaicin, the pungent ingredient of red peppers, has a neurotoxic effect on afferent fibers and destroys the majority of C-fibers in rodents when administrated neonatally (Fitzgerald 1983; Hiura 2000; Holzer 1991; Szallasi 1994). Capsaicin-induced C-fiber depletion causes expansion of excitatory receptive fields and alters neuronal properties in spinal (McMahon and Wall 1983; Wall et al. 1982), trigeminal (Kwan et al. 1996, 1999), and barrel cortical cells (Nussbaumer and Wall 1985; Wall et al. 1982). Consistent with these findings, other studies have shown that acute administration of capsaicin causes an expansion of the excitatory receptive field size of cells in DCN (McMahon and Wall 1983) and neocortex (Calford and Tweedale 1991; Greek et al. 2003; Katz et al. 1999). However, little is known about the

effects of C-fiber depletion on inhibitory receptive fields of cortical barrel cells. In the present study, we used electronically controlled mechanical displacement of paired whiskers to quantitatively examine the AW-evoked inhibition of barrel cells in normal and C-fiber-depleted rats.

Materials and methods

Animal preparation

Twenty-two adult, male, albino rats (Sprague–Dawley strain) weighing 250–400 g were used in this study. All procedures conformed to animal care and use guidelines of Neuroscience Research Center of Shaheed Beheshti University. Ten rats were neonatally treated with capsaicin (Cap) and the others were vehicle-treated (Con). The capsaicin injection solution was prepared by mixing a solution of 5% capsaicin (Sigma) in ethanol with Tween 80 and 0.9% saline in a ratio of 1:1:8 by volume, respectively. The vehicle solution consisted only of ethanol, Tween 80, and saline. Neonatal rats received an intra-peritoneal injection of either capsaicin solution (50 mg kg^{-1}) or its vehicle within 24 h of birth. It has been shown in many studies that neonatal treatment of rats with this dose of capsaicin within 48 h after birth results in effective depletion of C-fiber afferents (Fitzgerald 1983; Hiura 2000; Holzer 1991; Szallasi 1994). Corneal chemosensitivity (Krahl et al. 2001) was used in this study as an additional test to assess the effectiveness of capsaicin treatment. One drop of 1% ammonium hydroxide was applied to the right eye of adult animals and the number of times they wiped their right eye in the first 10 s after application was counted. The corneal chemosensitivity was significantly reduced in the capsaicin-treated

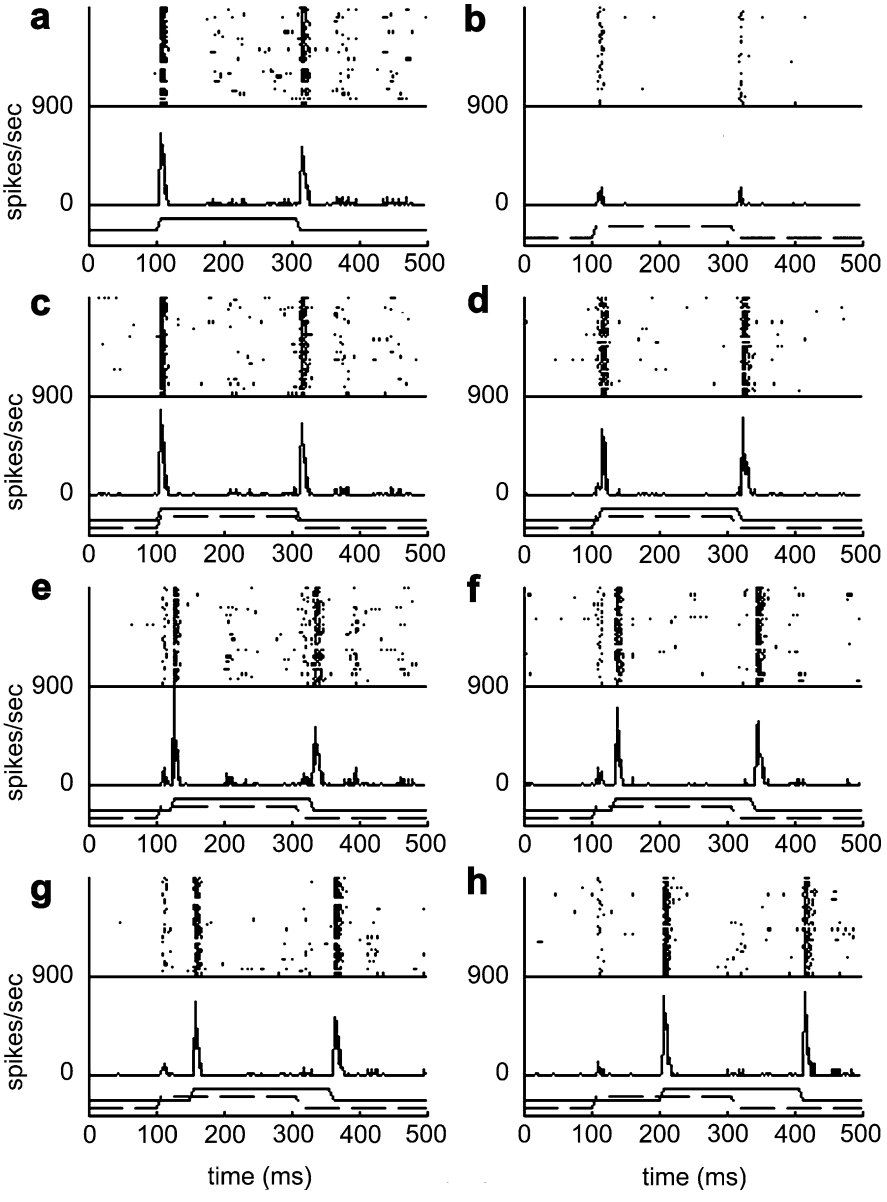

Fig. 1 Responses of a neuron in the capsaicin-treated group (neuron C12D2N4) to the eight deflection patterns. (**a**) main whisker deflection. (**b**) adjacent whisker deflection. (**c**)–(**h**) combined deflection of main and adjacent whiskers with inter-deflection intervals of 0, 10, 20, 30, 50, and 100 ms, respectively. The stimulus trace is shown below each graph. The *solid line* presents the main whisker deflection and the *dashed line* presents displacement of the adjacent whisker. *Upper* and *lower* halves of each graph are raster plot and peri-stimulus time histogram, respectively. PSTH bin size is 1 ms

(3.6±1.05) compared with the vehicle-treated (14.6±0.87) rats (*t*-test, $P<0.001$). Since chemosensitivity information is mainly transmitted through C-fibers (Holzer 1991), the reduction in chemosensitivity confirms the effective depletion of C-fiber afferents.

On each day of the electrophysiological experiment, one of the rats in the Cap or Con groups was randomly selected and anesthetized by intra-peritoneal injection of urethane (1.5 g kg^{-1}). Heart rate, respiration rate and rectal temperature were regularly monitored. The animal was mounted in a stereotaxic apparatus and a craniotomy was made over SmI vibrissa cortex from 1 to 4 mm posterior to bregma and 4 to 7 mm lateral to midline. During the experiment cortical surface was covered by 3% agar solution in saline. If required, supplementary doses of anesthetic were administered to maintain the depth of anesthesia throughout the recording.

Physiological recording and vibrissa stimulation

Electronically controlled mechanical stimulations were used to deflect either one whisker or two whiskers independently. The stimulator was constructed using two loudspeakers. One end of a thin glass tube (inner diameter: 0.69 mm, outer: 1.2 mm) was fixed on the center of each speaker. By controlling the electrical voltage delivered to the speakers, we were able to independently displace the other end of glass tubes by 700 μm in 7 ms (an average speed 100 mm s^{-1}). The accuracy of displacements was verified using microscopic measurements.

Whiskers were trimmed to a length of 10 mm and were inserted into the free ends of the stimulator tubes which were 5–6 mm from the base of whiskers. Individual stimuli consisted of a 700 μm deflection over 7 ms followed by a hold phase of 200 ms duration. Deflections were always in a ventrodorsal direction. Whiskers returned to rest position at the same speed of deflection.

A glass microelectrode with a tip diameter of 2–5 μm filled with 3 mol L^{-1} NaCl solution was used to record the activity of barrel cortical neurons. Microelectrodes were oriented normal to the cortical surface and advanced into the barrel cortex by a custom made microdrive with a precision of 1 μm. Single neuron action potentials were isolated using an amplitude window discriminator (WPI, UK) and the accuracy of isolation was judged by spike waveform and amplitude criteria. After isolation of a neuron in layer IV of barrel cortex, its receptive field was determined using hand-held probes. The whisker whose displacement generated the most vigorous neural response with the shortest response latency was taken as the main whisker and the whisker caudal to it as an adjacent whisker. In addition to electrophysiological criteria that were used to ensure precision of single unit isolation, Inter-spike Intervals were calculated in the first 50 ms after deflection of the main whisker. In all the recording sites average Inter-spike Intervals were significantly above 1 ms (one-tailed *t*-test, $P<0.05$).

To study responses of barrel cortex neurons to combined stimulation of two vibrissae in capsaicin-treated and control animals a conditioning-test paradigm (Simons 1985) was used. In our conditioning paradigm adjacent and main whiskers were deflected successively with time intervals between their stimulation varying in steps of 0, 10, 20, 30, 50, and 100 ms (Fig. 1). Main and adjacent whiskers were also stimulated alone to obtain a baseline measure of the neural response to the deflection of individual whiskers. For each isolated neuron these eight stimulation patterns (two single and six combined whisker deflections) were repeated 40 times in random order. The starts of stimulation patterns were separated by 1000 ms in successive trials. Stimulus delivery was controlled by a PC (Pentium MMX 233 MHz) running homemade software. The same program was responsible for storage of spike times and stimulus type and timing.

At the end of data collection sessions, recording sites were marked by electrolytic lesions (anodal current, 5 μA, 10 s). The animal was perfused by normal saline and then formalin in phosphate buffer, its brain was removed and placed in 10% formaldehyde. After fixation, the brain was cut into 60–80 μm slices and recording positions were confirmed after Nissl staining.

Data analysis

Controlled electromechanical stimulation of vibrissae enabled quantitative analysis of capsaicin treatment effects on neural responses to combined stimulation of adjacent and main whiskers. Stimulus aligned peristimulus time histograms (PSTHs) were constructed (1 ms bin duration) for each of the eight stimulation patterns delivered to a neuron. Neural response onset latencies of main and adjacent whiskers were determined by analyzing the PSTHs of solitary deflection of main and adjacent whiskers, respectively. Onset latency was defined as the first of three consecutive 1 ms bins after whisker displacement at which the spike probability exceeded the mean+3.29×SD (i.e. $P<0.001$) of activity measured in a control period 100 ms before stimulus onset. Average firing rates to solitary deflection of main and adjacent whiskers were calculated for a 10 ms period following response onset latencies of main and adjacent whiskers respectively. Response peak latency was determined as the bin with the highest spike probability after onset latency. Similar criteria were used to calculate main whisker response latencies after deflection of main whisker in combined stimulation patterns. The same parameters as used for calculating properties of neural response to stimulus onset (ON response) were used to calculate those of stimulus offset (OFF response).

The facilitation index (Shimegi et al. 1999) was used to quantitatively assess the effects of combined whisker stimulation on neural response magnitude to main whisker deflection. Facilitation index (FI) was defined as R_{com}/R_{sum}, where R_{com} is the average firing rate in a 10-ms window following main whisker response latency in a

combined stimulation pattern so that the offset of response window from adjacent whisker deflection was equal to the inter-deflection interval plus main whisker response latency, and R_{sum} is the summation of average firing rates elicited by stimulation of main and adjacent whiskers alone. The main whisker response magnitude used in the FI was calculated as described above and the adjacent whisker firing rate used in FI was measured in a 10-ms window whose offset from adjacent whisker deflection was equal to the offset of the R_{com} response window from adjacent whisker displacement in the combined stimulation pattern. FI values greater than 1.0 signify responses greater than a simple summation of responses to individual whisker stimulations (facilitative interaction) and values less than 1.0 indicate a proportional reduction in a cell's discharges compared with the linear summation (suppressive interaction). Qualitatively similar results were observed for different window widths. FI values for stimulus offset were calculated the same way as for stimulus onset.

Results

A total of 43 vibrissa-sensitive cells were recorded from the barrel cortex of 22 adult, male, Sprague–Dawley rats. Twenty-two of these neurons were isolated in ten capsaicin-treated animals (Cap) and the control group consisted of the other 21 neurons studied in 12 vehicle-treated rats (Con).

For each neuron the whisker whose deflection generated the highest neural response magnitude and the shortest response latency was considered as the main whisker and the whisker caudal to it as an adjacent whisker.

All cells in the capsaicin-treated group and 20 (95%) of cells in the control group elicited responses to both onset and offset of main whisker deflections. Unless otherwise mentioned, neural response properties reported in this study are obtained from neural responses related to whisker deflection onset. For deflection offset, these properties were qualitatively similar to those of stimulation onset.

A conditioning-test paradigm in which adjacent whisker deflection preceded that of main whisker was used to study the neural response changes due to vibrissae interaction. The studied intervals between stimulation of adjacent and main vibrissae were 0, 10, 20, 30, 50 and 100 ms.

Capsaicin effect on vibrissae interaction

For 15 neurons in the capsaicin-treated group and 17 neurons in the control group, all eight patterns of stimulation were applied 40 times in a random order. Figure 1 illustrates how responses of a neuron in the Cap group to main whisker deflections are modulated by variation of inter-deflection interval in combined stimulation patterns. For 0 ms inter-deflection interval, response magnitude is quite close to the response magnitude of solitary main whisker deflection. As inter-deflection interval increases response magnitudes of the main whisker decrease first and then increase back to the level of response magnitude of the 0 ms interval. Facilitation index (FI) was used to quantify the strength of vibrissae interaction (see Methods). FI is the ratio of the observed response magnitude after a combined deflection pattern to the magnitude expected by a linear summation of responses to single deflection of main and adjacent whiskers (see Methods). An FI value less than one, therefore, indicates a suppressive interaction of whiskers while an FI value greater than 1 shows a facilitative interaction. Figure 2 illustrates how FI alters on changing the inter-deflection interval in the capsaicin-treated and control groups.

A repeated-measure ANOVA was performed to investigate the effect of capsaicin-treatment and inter-deflection interval on facilitation index. The ANOVA showed a significant effect of both inter-deflection interval ($F_{(5,150)}$=15.3, $P<10^{-4}$) and capsaicin-treatment ($F_{(1,30)}$=9.2, $P<0.005$) and the interaction of these two factors was not significant ($F_{(5,150)}$=0.02, $P>0.9$). Figure 2 shows how capsaicin-treatment causes a rather homogeneous upward shift in FI values for all inter-deflection intervals. In order to investigate the source of capsaicin effects on FI values raw firing rates were evaluated. Spontaneous neural activity was statistically comparable between Cap and Con groups (t-test, $P>0.7$). It has been previously shown that neonatal treatment with capsaicin expands receptive fields of barrel cortex neurons (Wall et al. 1982; Nussbaumer and Wall 1985) and increases response magnitudes of these neurons to whisker deflections (Kiani et al., unpublished work). Similarly, in this study magnitude of responses to deflection of main and adjacent whiskers were higher in the Cap group compared with the Con group (t-test, $P<0.05$) and the ratio of the response magnitude of the adjacent whisker to that of the main whisker was statistically comparable between the

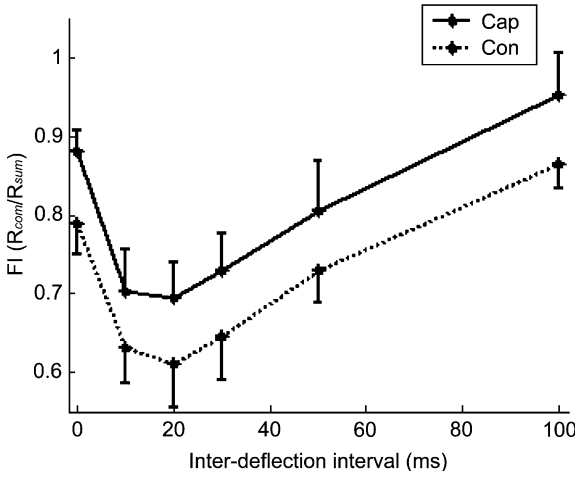

Fig. 2 Effect of inter-deflection interval on FI values in the Cap and Con groups. Capsaicin treatment causes a homogeneous increase of FI at all inter-deflection intervals. *Error bars* represent SEM

two groups (*t*-test, $P>0.6$). Therefore, the increased FI in capsaicin-treated rats is not due to a decrease in the denominator of the ratio. Instead, this is caused by rise in the response magnitude to combined deflection of adjacent and main whiskers (R_{com}) so that the percentage change in R_{com} is larger than that in the summation of response magnitudes of the main and adjacent whiskers when deflected individually (R_{sum}). This increase in the FI values indicates a decrease in suppressive whisker interactions or/and an increase in facilitative interactions after capsaicin-treatment. Furthermore, this change in whisker interaction is not a function of inter-deflection interval. FI values of OFF responses (responses to stimulus offset) were close to those of ON responses (responses to stimulus onset) in the Cap group so that, for each inter-deflection interval, FI values of cells were statistically comparable for their ON and OFF responses (paired *t*-test, $P>0.1$).

Capsaicin effect on response time course

After deflection of main whisker alone, neural responses in either the capsaicin-treated or the control group had a median onset latency of 7 ms (Cap, mean±s.d., 7.7 ±1.5 ms; Con, mean±s.d., 7.9±1.4 ms). The onset latencies after deflection of adjacent whisker alone had a median of 11 ms in the Cap and 12 ms in the Con group. (Cap, mean ±s.d., 10.6±2.4 ms; Con, mean±s.d., 11.7±2.9 ms). A repeated-measure ANOVA revealed that while adjacent or main whisker deflection had a significant effect on response latency ($F_{(1,26)}=47.7$, $P<10^{-4}$), capsaicin treatment did not change response onset latencies (capsaicin treatment, $F_{(1,26)}=1.3$, $P>0.2$; interaction of capsaicin treatment and type of whisker, $F_{(1,26)}=0.5$, $P>0.4$). A Bonferroni post-hoc test showed that response latency of main whisker is less than that of adjacent whisker in both Cap and Con groups ($P<10^{-3}$), but response latency of main whisker in the capsaicin-treated group was not different from that in the control group and there was also no significant difference between Cap and Con groups in response onset latency after adjacent whisker deflection ($P>0.5$). Similar results were obtained using response peak instead of onset latency (ANOVA, type of whisker, $P<10^{-4}$, capsaicin treatment, $P>0.8$, interaction, $P>0.9$).

Response latencies to deflection of main and adjacent whiskers, in our data, differ by about 5 ms. Therefore, when adjacent and main vibrissae are deflected simultaneously (0 ms inter-deflection interval), it can be expected that neural response in the first 5 ms after response latency is not affected by main and adjacent vibrissae interaction. Figure 3 depicts the FI values for the first and second 5-ms bins after response latency for the simultaneous deflection of the two whiskers (left-most points in Fig. 2). The main increase in FI, after C-fiber depletion, happens in the second 5-ms bin where FI increases from 0.55 in Con group to 0.75 in Cap group (37% increase) compared with the first bin where FI increases from 0.89 to 0.99 (11% increase). Evaluation of raw response magnitudes revealed

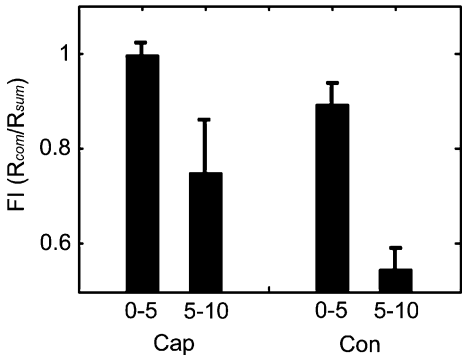

Fig. 3 FI values for the first and second 5-ms periods after response onset following simultaneous deflection of main and adjacent whiskers. In both Cap and Con groups FI is lower by 5–10 ms after response latency compared with the initial 5 ms period (*t*-test, $P<0.05$). Capsaicin treatment mainly changes the FI values in the second 5-ms bin (37%) compared to the first one (11%)

that for solitary deflection of the main whisker the second 5 ms of response is affected more than the first 5 ms. While the response magnitude in the first 5 ms following response latency increased from 1.3±0.5 spikes (mean±s.d.) in the control groups to 1.5±0.6 spikes in the capsaicin-treated group (~15% increase), in the second 5 ms the increase was from 0.3±0.3 spikes in the Con group to 0.5 ±0.3 spikes in the Cap group (~67% increase). Also, the relative increase in responses to adjacent whiskers was higher in the second 5 ms period compared with the first. A similar pattern of increase, with more accentuation on difference of first and second bins, was observed for combined deflection of main and adjacent whiskers with 0-ms inter-deflection interval. In the first bin, capsaicin boosted responses from 1.3±0.5 spikes in Con to 1.6±0.6 spikes in Cap (~23% increase) and in the second bin the rise was from 0.3±0.3 to 0.6±0.4 spikes (~100% increase).

Figure 4 illustrates the effect of adjacent and main vibrissae interaction on response latency in the Cap and Con groups. Both onset and peak latencies had a minimum in 10 ms inter-deflection interval. Because measurement of peak latency is not affected by an overlap in neural

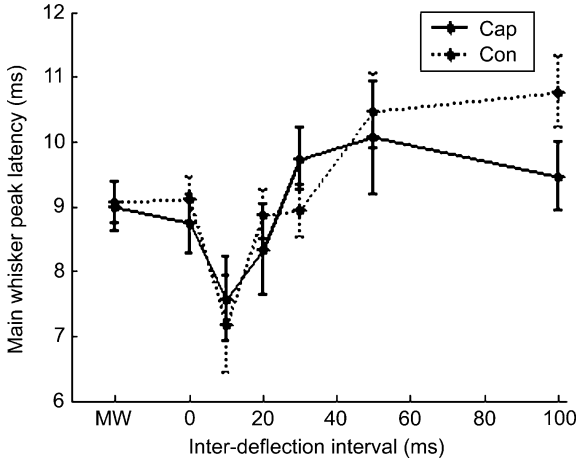

Fig. 4 Effect of adjacent and main whisker inter-deflection interval on peak latency of neural response to main whisker deflection. *Error bars* represent SEM. (*MW*: main whisker deflection alone)

responses to adjacent and main whiskers, it provides a more accurate estimate of the effects of inter-deflection interval and capsaicin-treatment on response latency in our conditioning paradigm. Inter-deflection interval had a significant effect on response latency (repeated-measure ANOVA, $F_{(5,150)}=6.9$, $P<10^{-5}$), but capsaicin-treatment did not cause a change in peak latencies in the conditioning paradigm ($F_{(1,30)}=0.2$, $P>0.4$). Also, capsaicin-treatment and inter-deflection interval had no significant interaction ($F_{(5,150)}=0.5$, $P>0.7$).

Discussion

In the present study we examined the effect of C-fiber depletion on barrel cortex single-cell responses to paired whisker displacements. Our data show that displacement of the adjacent whisker (AW) before main whisker (MW) stimulation suppresses the responses to MW stimulation in normal rats. This result is in agreement with previous findings (Brumberg et al. 1996; Simons 1985; Simons and Carvell 1989). The suppressive effect of multiple whisker stimulation is suggested to be due to an intra-cortical inhibition (Goldreich et al. 1999; Mirabella et al. 2001). It has been further suggested that this inhibitory effect is generated within layer IV of a single barrel and is not due to the interaction between neighboring barrels (Goldreich et al. 1999; Simons and Carvel 1989). The alternative view is that the barrel cells' receptive fields are shaped by horizontal connections between multiple neighboring barrels involving inhibitory circuitries (Armstrong-James et al. 1991; Fox 1994).

A GABA-mediated differential inhibitory effect has been shown for ON and OFF responses in rat barrel cortex (Kyriazi et al. 1996). In our study there was no major difference between the response modulations to stimulus onset and offset in Con and Cap groups. A difference would have been expected if C-fiber depletion alters such GABA inhibition in the barrel cortex. Further experiments such as measurement of barrel cortex GABA level in C-fiber-depleted rats are needed to address the possibility of GABA-mediated role in paired whisker interactions observed in the capsaicin-treated rats of the present experiments.

Potential source of the inhibitory circuitry affected by capsaicin treatment

Our results that depletion of C-fibers reduces the suppressive effect of paired whisker stimulation at all of the tested inter-stimulus intervals suggest that neonatal C-fiber depletion reduces the AW-evoked inhibition within the barrel cortex. It has been previously reported that such inhibitory interactions between MW and AW stimulation is rather weak, or not present, in the subcortical structures. For example Simons and Carvell (1989) have shown that multiple-whisker stimulation generates far less inhibitory interaction in the thalamic bareloides than the cortical barrels. In the light of this evidence it is plausible that capsaicin treatment also affects cortical inhibitory circuitries of layer IV barrel cortex. But a comparison of cortical and subcortical effects of capsaicin treatment is needed to directly address this issue. Our result further shows that the inhibitory mechanism is more strongly activated when whiskers are stimulated sequentially, the degree of inhibition being a function of the temporal pattern of multiple whisker stimulation.

Implications for object recognition

The surface properties of objects (i.e. texture and 3D structure) activate multiple whiskers with different spatiotemporal patterns. Integration of information from multiple whisker stimulation could be used for object identification and recognition. It is possible that the time-dependent AW evoked inhibition act as a gating mechanism, which controls the input from layer IV to layer II/III cells. These inputs are known to be critical for shaping the receptive field properties of layer II/III cells (Armstrong-James and Fox 1987; Armstrong-James et al. 1992). Such a gating mechanism might be essential for mapping the surface and 3D structural properties of objects on to an object-specific spatiotemporal pattern of activity across cortical barrels. The C-fiber dependent inhibitory mechanism evoked by AW stimulation could modulate the response properties of MW layer II/III cells by putting constraints on the type of activity that can pass through layer IV to other barrel layers.

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