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Research report

Effects of neonatal C-fiber depletion on discrimination of principal and adjacent whisker stimulation within rat individual cortical barrels

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Abstract

Controlled mechanical displacement was used to stimulate single whiskers in normal and C-fiber depleted rats to quantitatively examine the role of C-fibers in the response properties of barrel cortical cells. C-fiber depletion using neonatal capsaicin treatment increased the barrel single-unit response magnitude to deflection of both principal and adjacent whiskers while there was not any significant difference in the barrel cells' spontaneous activity. Capsaicin treatment increased the neural response duration of adjacent whisker stimulation but did not change that to the principal whisker deflection. There was no difference in response latencies of principal or adjacent whisker displacement between the normal and C-fiber-depleted groups. The efficiency of neural code for differentiation of principal and adjacent whiskers was measured by ROC analysis, which reflects the performance of an ideal observer in this discrimination using cells' firing rate. No significant difference was found in the performance of neurons in capsaicin-treated and control groups in distinguishing principal and adjacent whisker deflections from each other. These results suggest that neonatal C-fiber depletion causes an expansion of barrel cells receptive field but it does not affect the discrimination of individual whisker stimulation by the barrel cells.

Theme: Sensory systems
Topic: Somatosensory cortex and thalamocortical relationship

Keywords: Barrel cortex; Rat; Capsaicin; Whisker discrimination

1. Introduction

The receptive field properties of low-threshold mechanical somatosensory cells in the central nervous system are influenced by C-fibers [2,10,12,16,17,19]. Capsaicin, the pungent ingredient of red peppers, has a neurotoxic effect on afferent fibers and destroys C-fibers in rodents when administrated neonatally [4,8,9,18]. Capsaicin-induced C-fiber depletion causes expansion of excitatory receptive fields and alters neuronal response properties in rat spinal [14,19], trigeminal [12,13] and barrel cortical cells [16,19]. Cortical barrels are anatomically discrete clusters of cells in rodent somatosensory cortex [22]. Barrel cells respond to whiskers on the contralateral face [20] and receive converging thalamocortical inputs from multiple whiskers [15,23]. Deflection of the principal whisker (PW) evokes higher discharge rates with lower response latencies compared to adjacent whiskers (AW) [1,21]. The distinct organization of rat barrel cortex and the ability to independently stimulate its principal and adjacent receptive fields makes it a suitable model for studying the effect of C-fiber depletion on center and surround receptive field organization of somatosensory cells. For example, a pioneer study by Wall et al. [19] has shown that C-fiber depletion by neonatal capsaicin treatment increases the receptive field size of the barrel cortical cells. In a more recent study, Kwan et al. [12,13] have shown that neonatal capsaicin treatment increases receptive field size of cells in rat trigeminal nucleus principalis.

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Consistent with these findings, other studies have shown that acute inactivation of C-fibers by local subcutaneous injection of capsaicin causes an expansion of the excitatory receptive field size of cells in DCN [14,17], thalamus [10] and neocortex [2,6,10] probably by unmasking new tactile responses.

However, little is known about the effects of C-fiber depletion on the neural code responsible for the discrimination of principal and surround whisker deflection. In addition, in the previous studies of barrel cell responses in C-fiber-depleted rats, the stimulations were not quantitatively controlled, making it difficult to assess and compare the responses in different groups. To address these questions, we used electronically controlled mechanical displacement of individual whiskers to quantitatively examine the barrel cell responses to PW and AW stimulation in normal and C-fiber-depleted rats.

2. Materials and methods

We recorded the activity of single neurons in the barrel cortex of 22 adult, male, Sprague–Dawley rats weighing 250–400 g. All of the procedures were in accordance with guidelines for the care and use of laboratory animals of Neuroscience Research Center at Shaheed Beheshti University and complied with guidelines of N.I.H.

2.1. Capsaicin treatment

Capsaicin powder (Sigma) was dissolved in a solvent consisting of ethanol, Tween 80 and 0.9% saline in a ratio of 1:1:8 to prepare a 0.5% solution of capsaicin. The vehicle solution was made up of only the capsaicin solvent. Rat neonates received an intraperitoneal injection of either capsaicin solution (50 mg/kg) or its vehicle in the first postnatal day and then were allowed to grow to adulthood. Ten capsaicin-treated (Cap) and 12 vehicle-treated rats (Con) were used in our experiments. Treatment of neonatal rats with capsaicin (50 mg/kg) within 48 h of birth effectively destroys C-fibers [4,8,9,13,18]. Efficacy of capsaicin treatment in depleting C-fibers was also assessed in this study by corneal chemosensitivity test [11]. Corneal chemosensitivity is principally mediated by C-fibers [9] and its significant reduction, as in our experiment, means significant depletion of C-fibers. The number of times that capsaicin-treated animals wiped their eyes after administration of one drop of 1% ammonium hydroxide into their eyes was significantly reduced compared to vehicle-treated rats (Cap, mean ± S.D. 3.6 ± 1.05; Con, mean ± S.D., 14.6 ± 0.87; t-test $p < 10^{-7}$).

2.2. Animal preparation

Animals were anesthetized by urethane (1.5 g/kg, i.p.) and mounted in a stereotaxic head-holder device. A hole 1–4 mm posterior and 4–7 mm lateral to bregma was drilled in the skull to expose barrel cortex. Throughout the surgery and electrophysiological recording, rectal temperature, respiration rate and heart rate were regularly monitored. Temperature was maintained at 37.0–38.0 °C. Regularity of respiration and absence of spontaneous movement was ensured. Whenever necessary, additional doses of urethane (1/3 to 1/4 of induction dose) were used to maintain the level of anesthesia. Agar solution (3%) in saline was used to cover cortical surface throughout the experiment.

2.3. Vibrissa stimulation

Electronically controlled mechanical stimulation was used to deflect principal and adjacent whiskers (see below) independently. The stimulator consisted of two loud speakers that were attached at the center to two glass tubes (inner diameter: 0.69 mm, outer diameter: 1.2 mm). By controlling the electrical voltage delivered to each speaker, we were able to independently displace the other end of glass tubes by 700 μm at an average speed of 100 mm/s. The accuracy of displacements was verified using microscopic measurements. 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.

2.4. Electrophysiological recording and data acquisition

Single neural activity was recorded extracellularly by glass microelectrodes with tip diameters of 2–5 μm. Electrodes were filled with 3 M NaCl solution and were lowered perpendicular to cortical surface into the barrel cortex by a custom-made microdrive (1-μm precision). Acquired signal was amplified and filtered using standard equipment. We isolated single neuron action potentials at the level of layer IV (depth of 450–780 μm) by an amplitude window discriminator (WPI, UK). Spike waveform, amplitude and time course were closely monitored throughout recording to ensure precision of isolation. When a single unit activity was reliably isolated, whiskers contralateral to the recorded cortex were manually deflected using handheld probes. After this qualitative assessment of neural receptive field, electronically controlled mechanical stimulation was used to stimulate whiskers that evoked a neural response. For controlled stimulation, whiskers were cut to a length of 10 mm from the base and were inserted into the stimulator tubes that were placed at a distance of 5–6 mm from the base of whiskers. The whisker that elicited the strongest response with the shortest latency was defined as principal whisker and the whisker caudal to it as an adjacent whisker. For the data presented in this paper, stimulator deflected principal or adjacent whiskers in a random order for 40 times at a frequency of 1 Hz. A homemade computer program controlled the stimulus delivery and stored neural

spike times. Using this program, we were able to monitor stimulus aligned peristimulus time histograms of neurons in real time and calculate neural response latency and magnitude online.

At the end of each data collection session, the animal was perfused and its brain was placed in 10% formaldehyde. After fixation, the brain was cut into 60–80 μm slices and recording sites—that were marked by electrolytic lesions (anodal current, 5 μA, 10 s) after recordings—were confirmed after Nissl staining.

2.5. Data analysis

For each neuron, peristimulus time histograms (PSTH) of principal and adjacent whisker deflections were constructed (bin size, 1 ms). Neural response latency threshold was defined as mean + 3.29 × S.D. (i.e., $p < 0.001$) of spontaneous activity measured in a 100-ms period before stimulus onset. Response latency was then determined as the first bin after start of whisker deflection, at which spike probability exceeded latency threshold for three consecutive bins. Response duration was defined as the number of 1-ms bins that remained above latency threshold after response latency. Response magnitude was calculated as the average firing rate over a 25-ms window following response latency. Different window widths (from 7 to 50 ms) produced very similar results and 25 ms was chosen because it was well above the mean of response duration (mean ± S.D., 13 ± 8 ms, median, 12 ms) (*t*-test, $p \ll 10^{-8}$) and corresponded to the 90th percentile of response durations. 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).

A receiver-operating characteristics (ROC) analysis [3,7] was used to determine the effects of neonatal treatment with capsaicin on discriminability of principal and adjacent whiskers based on differential neural activity to deflection of these whiskers. Here, the ROC plot is the graph of hit rate vs. false alarm, defined for different threshold values, in the task of classifying the neural activity as one elicited by deflection of principal whisker or one caused by deflection of adjacent whisker. ROC area under curve values could be interpreted as the performance of an ideal observer in a two-alternative forced choice task; values around 0.5 indicate chance level classification (random guessing) while values of 1 and 0 indicate error-free classification. Thus, the ROC area is a measure of discrimination reliability of principal from adjacent whisker based on the neural activity. The initial 25 ms of neural response, which was used for measurement of response magnitude, was used to calculate the ROC area under curve. To determine the time course of principal from adjacent whisker discrimination, we used a sliding ROC analysis [5]. In this analysis, for each neuron, ROC area under curve was computed over a 10-ms window that was slid in 1-ms steps from 100 ms before stimulation to 200 ms after it. The ROC areas at each point were compared between Cap and Con groups to see how capsaicin treatment affects time course of principal/adjacent whisker discrimination. Qualitatively similar results were obtained using windows of various widths.

3. Results

The experiment was performed on 22 adult, male, albino rats (Sprague–Dawley) that had been neonatally treated with either capsaicin or its vehicle. We recorded the activity of 43 vibrissae-sensitive neurons in the barrel cortex of these animals [22 neurons in 10 capsaicin-treated (Cap) and 21 neurons in 12 vehicle-treated (Con) rats]. The principal whisker of each neuron was determined as the whisker that, when deflected, elicited the most vigorous neural response with the shortest response latency. The whisker located caudal to the principal whisker was taken as an adjacent whisker. Electronically controlled mechanical stimulation of vibrissae enabled us to accurately define how neural responses to principal or adjacent whisker deflections were influenced by C-fiber depletion.

3.1. Neural response properties of single vibrissa stimulation

Response onset latencies to principal and adjacent whisker deflections in the capsaicin-treated and control groups are shown in Table 1. A two-way ANOVA was performed to investigate the effect of capsaicin treatment and adjacent/principal whisker deflection on response latency. While the effect of the latter factor was significant ($p < 10^{-7}$), no significant effect was observed for capsaicin treatment or the interaction of the two factors ($p > 0.2$). Response latencies of either principal whiskers or adjacent whiskers were statistically equal in the Cap and Con groups (Bonferroni, $p > 0.5$). On the other hand, in both capsaicin-treated and control groups, neural responses to adjacent whisker deflection started later, compared to the principal whisker (Bonferroni, $p < 0.001$) (Figs. 1 and 2).

Capsaicin treatment increased the duration of neural response to deflection of adjacent vibrissae but did not change response duration after principal whisker stimulation (Fig. 3). Response duration of adjacent whisker was significantly higher in the Cap compared to the Con group (*t*-test, $p < 0.05$, Bonferroni corrected). Consequently, there was no significant difference in response durations after principal

Table 1
Neural response latency to deflection of principal and adjacent vibrissae in the capsaicin-treated and control groups

	Principal whisker		Adjacent whisker	
	Mean ± S.D. (ms)	Median (ms)	Mean ± S.D. (ms)	Median (ms)
Capsaicin-treated	7.7 ± 1.5	7	10.6 ± 2.4	11
Control	7.9 ± 1.4	7	11.7 ± 2.9	12

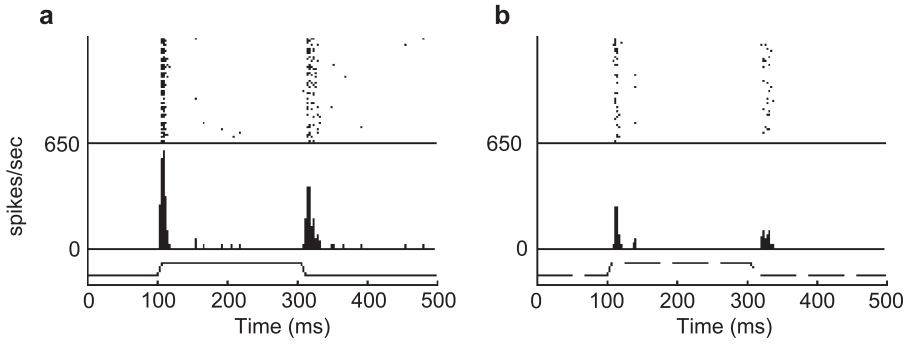

Fig. 1. Responses of a neuron in the Cap group to displacement of principal (a) and adjacent (b) whiskers. The upper half of each graph is the raster plot of neural response over 40 stimulations. The lower halves represent PSTHs. Stimulus waveform is shown below the PSTH.

and adjacent whisker deflection in the Cap group (paired *t*-test, $p>0.7$). But response duration of principal vibrissae was significantly higher than that of adjacent whisker in the control group (paired *t*-test, $p<0.01$).

The magnitude of neural responses to deflection of principal whisker was higher than that to adjacent whisker stimulation in both capsaicin-treated and control rats. A two-way ANOVA on response magnitudes with capsaicin treatment and principal/adjacent whisker deflection as main factors showed a significant effect of both factors ($p<0.02$) without any significant interaction between factors ($p>0.9$). Fig. 4 illustrates how neural responses to both principal and adjacent vibrissae deflection increases due to capsaicin treatment. However, spontaneous neural activity was not different between Cap and Con groups (Con, mean ± S.D.: 2.25 ± 2.84 spikes/s; Cap, mean ± S.D.: 1.97 ± 2.11 spikes/s, $p>0.7$).

In addition to analyzing the effects of neonatal capsaicin treatment on neural responses elicited by deflection of whiskers (ON responses), we analyzed capsaicin effects on neural responses generated by the return of whiskers from deflected position to the rest position (OFF responses). Like ON responses, capsaicin treatment increased duration of OFF responses to adjacent whiskers ($p<0.01$) without changing that of principal whiskers ($p>0.7$). Response durations of ON and OFF responses were statistically comparable. A three-way ANOVA with ON/OFF response, adjacent/principal whisker and capsaicin treatment as main factors showed a significant effect of the two latter factors ($p<0.05$) without a significant effect of the first factor ($p>0.2$) on response duration. Similar to ON response magnitude changes, OFF response magnitudes for adjacent and principal whiskers were increased by capsaicin treatment. A two-way ANOVA showed a significant effect for both capsaicin treatment and adjacent/principal whisker on OFF response magnitudes ($p<0.05$). Response magnitudes for ON and OFF responses were statistically comparable ($p>0.6$) as revealed by a three-way ANOVA with main factors similar to that used for response duration. Finally, a two-way ANOVA on OFF response latencies showed significant effect for both adjacent/principal whisker deflection ($p<10^{-7}$) and capsaicin treatment ($p<0.05$) without any interaction between factors ($p>0.9$). Response latencies of OFF responses were comparable to that of ON responses ($p>0.7$) as revealed by the three-way ANOVA.

3.2. Capsaicin effect on differentiation of vibrissae by neurons

In this study, C-fiber depletion due to neonatal treatment of rats with capsaicin resulted in an increase in neural response magnitudes after deflection of both principal and adjacent whiskers. Other studies have also shown an expansion in the receptive field size of neurons in the barrel cortex [19] and trigeminal nucleus principalis [13] after neonatal capsaicin treatment. Does this expansion in receptive field

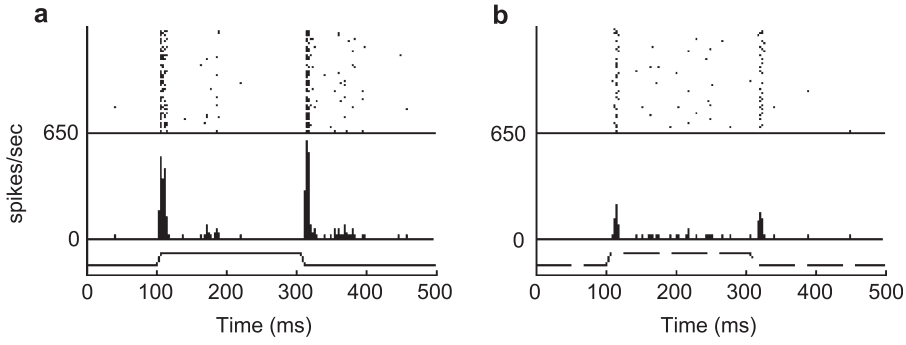

Fig. 2. Responses of a neuron in the Con group to displacement of principal (a) and adjacent (b) whiskers. Conventions are as in Fig. 1.

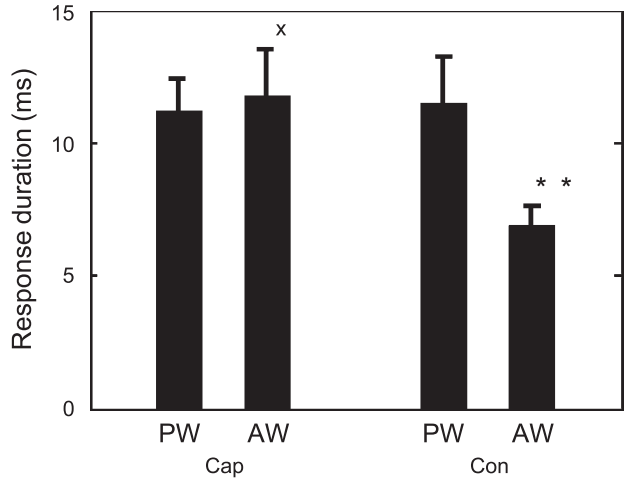

Fig. 3. Neural response duration after deflection of principal and adjacent whiskers in the capsaicin-treated and control rats. Error bars represent S.E.M. Significant differences between PW and AW within Cap or Con groups (e.g., AW vs. PW of Con) are shown by asterisk (*, $p<0.05$; **, $p<0.01$) and significant differences between same whisker types of Cap and Con groups (e.g., AW of Cap vs. AW of Con) are indicated by cross ($\times$, $p<0.05$; $\times\times$, $p<0.01$). PW: principal whisker; AW: adjacent whisker; Cap: capsaicin-treated group; Con: control group.

size of neurons disrupt the segregation of principal and adjacent whiskers by neurons? The efficiency of neural responses for differentiation of principal and adjacent whiskers was measured by ROC analysis (see Materials and methods), which reflects the performance of an ideal observer in this discrimination using neuron's firing rate. For the 25-ms window following response latencies of principal and adjacent whiskers of each cell, no significant difference was found in the performance of neurons in the capsaicin-treated (ROC area under curve, mean $\pm$ S.D., 0.76 ± 0.16) and control (ROC area under curve, mean $\pm$ S.D., 0.74 ± 0.18) groups in distinguishing principal and

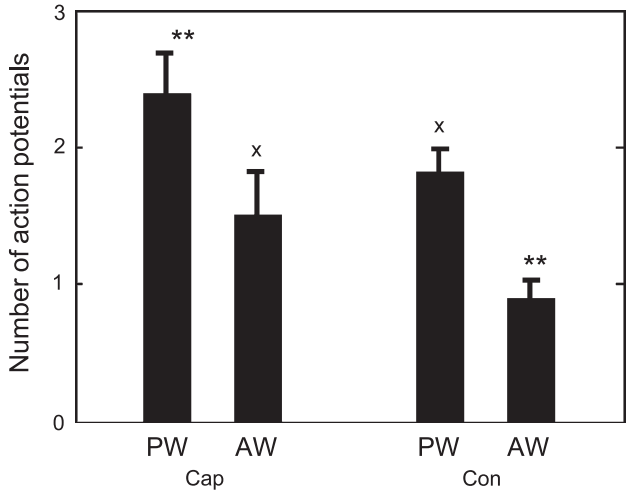

Fig. 4. Neural response magnitude after deflection of principal and adjacent whiskers in the capsaicin-treated and control rats. Error bars represent S.E.M. Conventions are the same as in Fig. 3.

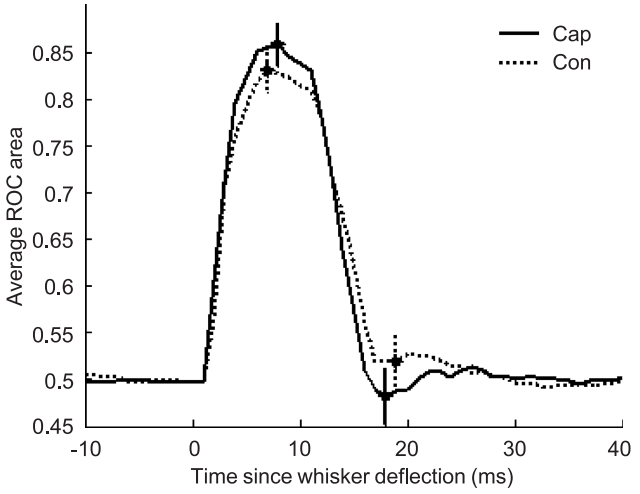

Fig. 5. Time course of principal from adjacent whisker differentiation in the capsaicin-treated and control groups. The average ROC values were calculated for neurons in the Cap and Con groups over a 10-ms window sliding at 1-ms steps. ROC values around 0.5 show chance level performance in discriminating principal from adjacent vibrissae. ROC values of 1 and 0 indicate error-free discrimination. Error bars represent S.E.M.

adjacent whisker deflections from each other (t-test, $p>0.7$). This could be intuitively explained by the fact that the ratio of adjacent vibrissa response magnitude to that of principal vibrissa remains roughly constant after C-fiber depletion (t-test, $p>0.8$). Although the discrimination of principal and adjacent whiskers, by using the neural activity in the first 25 ms after response onset, is not affected by capsaicin treatment, it could still have affected the time course of principal/adjacent whisker segregation within or outside of the tested 25-ms window. Such a change in the time course of discrimination can change the sliding ROC curve of the Cap group compared to the Con group. However, no significant difference was found between the two sliding ROC curves as shown in Fig. 5. Note that, for both Cap and Con groups, maximum sliding ROC values are higher than the latency adjusted ROC values (see the above paragraph). This is mainly because of the fact that the 10-ms window used for sliding ROC analysis is not aligned with principal and adjacent whisker response latencies and ROC analysis can, therefore, take advantage of latency differences between principal and adjacent whiskers.

4. Discussion

In the present study, we examined the effect of C-fiber depletion on barrel single cell responses to principal and adjacent whisker displacements. The results show that neonatal capsaicin treatment increases the responses of barrel cortical cells to both principal (PW) and adjacent (AW) whisker stimulation but has no effect on spontaneous activity of the cells. Other studies have also shown that neonatal C-fiber depletion affects low-threshold mechanical

responses of somatosensory cortical cells [16,19]. For example, a study by Wall et al. [19] has shown that C-fiber depletion by neonatal capsaicin treatment increases the receptive field size of the barrel cortical cells. These authors have suggested that capsaicin treatment defocuses whisker-barrel spatial organization by expanding the receptive field of cortical cells [16]. In our study, we used controlled mechanical displacement, which allowed us to make quantitative comparison of the responses to PW and AW stimulations. The results show that neonatal capsaicin treatment causes similar increase in cell responses to AW and PW stimulation, suggesting that the increase in receptive field size could be due to a general increase in excitability of the barrel cells. Our findings further suggest that the change in receptive field properties of barrel cells does not necessarily lead to deterioration of the cells receptive field spatial resolution (see below).

ROC analysis of the barrel cell responses in our study show that performance of an ideal observer in distinguishing principal and adjacent whiskers from each other based on the neural response remains constant after C-fiber depletion. It is plausible that destruction of C-fibers causes responses to PW and AW to be multiplied by a similar gain factor. On the other hand, although this transformation of neural response does not affect the accuracy of the ideal observer of ROC analysis, it may affect a biological system that works by thresholds.

In C-fiber-depleted rats, neural responses to PW deflection increased in magnitude without any significant change in response duration, suggesting that in the absence of C-fibers more net excitatory input is received by barrel cells in the usual time course of activation. On the other hand, neural responses to AW displacement increased both in duration and magnitude after neonatal treatment with capsaicin.

In general, consistent results have been reported for the effects of capsaicin on the receptive field properties of somatosensory cells when local subcutaneous injection or neonatal systemic administration has been used. This suggests that the effect of capsaicin on receptive field properties of central somatosensory cells is mainly exerted by destruction of C-fibers and not by systemic actions of capsaicin. In the light of such evidence, it has been suggested that intact C-fibers exert a tonic inhibition that normally affects the receptive field properties of somatosensory cells mainly by limiting the extent of the receptive fields of such cells [2,6].

The protraction of AW responses might have cortical and/or subcortical origin. It has been shown that C-fiber depletion causes an expansion of receptive field size of subcortical cells. For example, Kwan et al. [12,13] have shown that neonatal capsaicin treatment increases receptive field size of cells in rat trigeminal nucleus principalis. It is not clear whether the effect of C-fiber depletion occurs only at the lower levels of the whisker–barrel system and is projected to higher levels or if the effect is more general, influencing neural networks at all levels of the system. Further studies are needed to address these questions.

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