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Recurrent inhibition in the cerebral cortex

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ABSTRACT

Neuronal activity can be modulated by endogenous control mechanisms that either facilitate or suppress it. With this idea in mind, we attempted to evaluate and correlate spinal neuronal activity with the amplitude of corticogram (ECoG) event related potentials (ERP) in the presence of nociceptive stimulation in rats. We evaluated the ERP in response to noxious stimuli, endogenous analgesic actions, different frequencies, and heterotopic nociceptive stimulation, as well as in conjunction with recordings from neurons in the spinal cord that are activated by noxious stimuli. Computational tasks enabled us to establish correlations between the amplitude of ERP and neuronal firing of cells in the spinal dorsal horn.

Our results show that the ERP amplitude could be modified by previous activity in the cerebral cortex, but the activity in the spinal cord did not change. Previous activity could originate spontaneously or could be driven by sensory stimulation.

A recurrent inhibitory cortical action is proposed that could explain the suppression of pain perception during electrical or magnetic transcranial stimulation, as well as during heterotopic stimulation.

This study aims to uncover a local recurrent inhibitory cortical action that could modify the sensory information.

1. Introduction

It is well recognized that the cerebral cortex is the final station in the integrative process of sensory perception. This property is only possible because the central nervous system contains different control systems located along the sensory pathway and in related structures. The controls of neuronal activity flux have varying levels of complexity in terms of transduction, codification, and transmission and involve both excitatory and inhibitory processes. These facilitator and inhibitory control processes have been studied extensively, yet they have not been fully explored. Cerebral cortex activity is widely analyzed using averages of evoked activities [1] spectral powers of the electroencephalogram [2,3], or the sources of cortical activity [4–6]. Moreover, the amplitude of evoked activity in the human cerebral cortex varies considerably during the sleep-wake cycle or in the presence of painful stimuli [1].

The transformation of environmental or internal stimulation starts at the sensory receptors and is carried to the spinal cord in the first relay of sensory information. Neurons in the dorsal portion of the spinal cord are involved in nociception and are a primary target of the descending anti-nociceptive control systems. This particular condition makes the spinal dorsal neurons an interesting population for studying incoming sensory information and the changes produced by facilitator and inhibitory nociceptive processes [7–10].

In this context, our paper seeks to establish a correlation between sensory input (evaluated by recording single neurons in the spinal cord) and cortical evoked potentials (evoked by nociceptive stimulation). Additionally, both spontaneous and sensory-evoked cortical activities were used to evaluate a suppressive cortical process inhibiting incoming sensory information. First, we electrically stimulated the paraventricular hypothalamic nucleus, which has been reported to reduce sensory activation of nociceptive fibers that innervate spinal cord neu-

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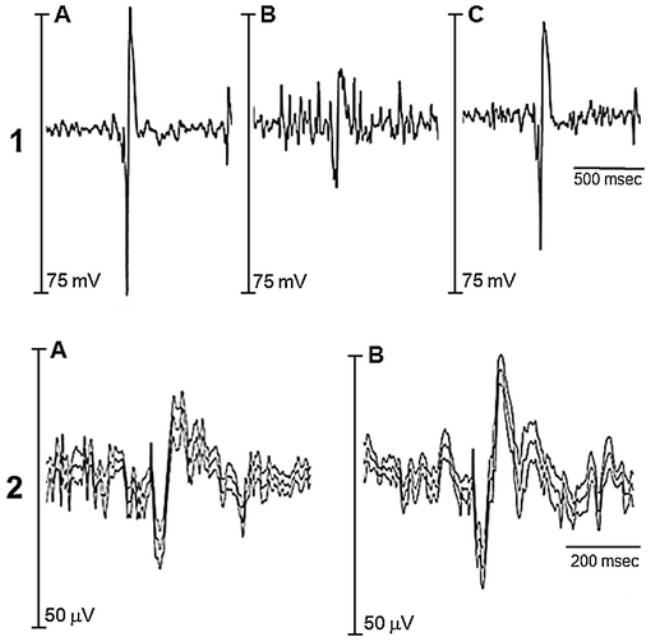

Fig. 1. Raw mean averaged of 20 ERP to nociceptive RF stimulations are shown. In 1A, mean averaged potentials in the control situation; in 2B, after electrical stimulation of the PVN; and in 2C, 10 min after PVN stimulation. In 2, the mean and standard deviation of ERP produced by the RF stimulation before (shown in 2A) and after the raphe magnus lesion in 2B. Notice the amplitude of the ERP in 2A and the enhancement of the ERP in 2B resulting from the raphe magnus lesion. This figure illustrates the utility of ERP in the evaluation of inhibitory mechanisms (1) and the effects of the suppression of an inhibitory mechanism (2).

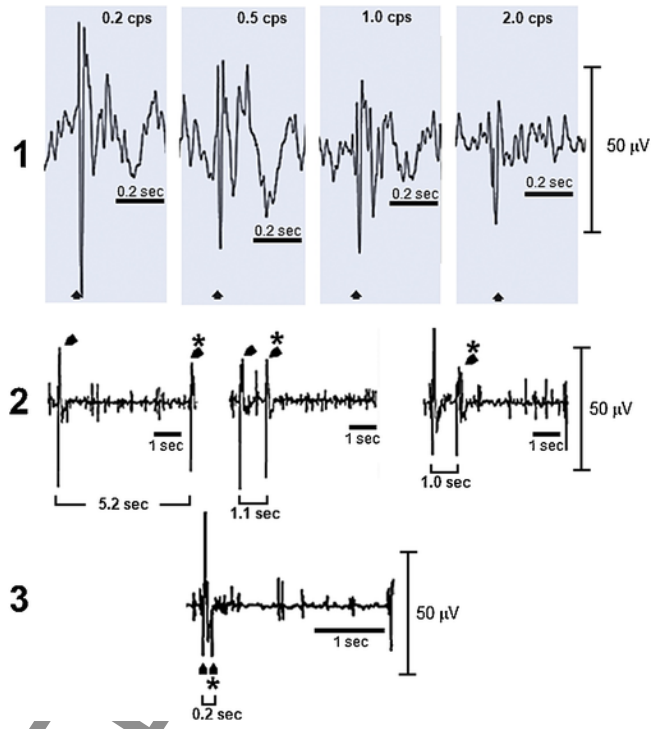

Fig. 2. In 1, averaged of raw (20 RF stimulations) ERP during the increase in frequency stimulation. The averaged ERP for 0.2, 0.5, 1 and 2 cps is illustrated. Notice the reduction in the ERP when the stimulation frequency increases. In 2, the mean averaged of raw ERP by heterotopic (upper and lower limbs) stimulation is illustrated. Arrows show the ERP of the RF electric stimulation located in the lower limb, and arrows with * show the ERP responses for upper limb stimulation. The interval between stimulation of the lower and upper limbs was reduced, and a partial diminution was observed in the upper limb ERP when the interval was approximately 1 s. Moreover, when the interval between the stimulation was 200 msec, the response for the upper limb was absent (in 3).

rons [11–13]. Next, to evaluate how cortical action regulates incoming sensory activity, we used computational tasks to assess the electrocorticogram (ECoG) amplitude and compare it with sensory input, which was considered as dorsal horn neuron responses to receptive field (RF) electrical stimulation.

2. Material and methods

We used rats provided by the Animal House of the Instituto de Neurobiología; they were housed in individual boxes with water and food *ad libitum* in a 12/12 h light/dark cycle and controlled temperature (23 + 3 °C).

All experimental procedures followed the Bioethical recommendations of the Instituto de Neurobiología, IASP ethical guidelines [14] the Guide for the Care and Use of Laboratory Animals established by the NIH, and ARRIVE guidelines for reporting experiments involving animals [15]

One hundred and forty-nine male Sprague-Dawley or Wistar rats, weighing between 280–310 g, were anaesthetized in a hermetic box with a mixture of 3.5% Sevoflurane or Halotane in a mixture of 1/3 oxygen and 2/3 nitric oxide, and after a loss of reflex, the rats were tracheotomized to deliver artificial respiration. The rats were maintained with artificial respiration throughout the experimental sessions. The rats were later placed in a stereotaxic apparatus using a spinal cord frame to fix the head and the spinal cord at the L2-L5 level. Two trephines at 9 mm AP, 4 mm L, and 3 mm AP, 4 mm L according to the Paxinos and Watson [16] stereotaxic atlas, were drilled in the skull to enable the ECoG recording with two silver balls. For the ECoG, filters were set between 0 to 300 Hz. Additionally, a laminectomy was performed to record from the L4-L5 spinal cord neurons and to reach the neurons receiving afferent input from the left lower limb. The data came from 149 rats (Sprague Dawley and Wistar) used in another series of experiments, in which we reported the effects of electrical stimulation of the paraventricular hypothalamic nuclei [8,17,18] on spinal cord neuronal responses. In these series of experiments, a concentric stainless-steel electrode (30 μm tip, 120 μm separation) was placed in the PVN in accordance with the stereotaxic atlas of Paxinos and Watson [16]. The electrode was located in an area between 2.1 and 1.6 mm caudal to bregma, 0.45 mm lateral to the midline, and 8.0 mm deep. In 6 experiments [17], a concentric stimulating electrode was placed on the raphe magnus (RMg) nucleus in order to compare the analgesic power between PVN and RMg. After surgery, the level of halothane was lowered to 2% to achieve an adequate level of anesthesia, which was continuously controlled by the presence of ECoG slow wave activity.

2.1. Recording procedures

Spinal cord extracellular unit recordings were made with 8–12 MΩ glass microelectrodes filled with pontamine blue at 5% in 1 M KCl solution. The electrodes were mounted in a microelectrode drive and were lowered into the spinal cord until they reached a stable level of neuronal activity. The specific receptive field [8,10,11,18] was located through gentle tactile stimulation (taps) until an activated neuron was found. Then, a pair of stainless steel electrodes was placed into the RF, and the intensity of electrical stimulation was increased to observe activation of A-beta and C-fibers in the recorded cell. The electrical stimulus consisted of single pulses of 1 msec at 0.2 Hz with intensity between 100 and 300 μA. As a general rule, we used the first 20 control stimulations for analysis. Wide dynamic range (WDR) neurons were identified by their responses to innocuous and noxious (strong pinch) mechanical stimuli and provided responses to A-beta and C-fiber stimulation applied to their excitatory RF on the left hind paw. Microelec-

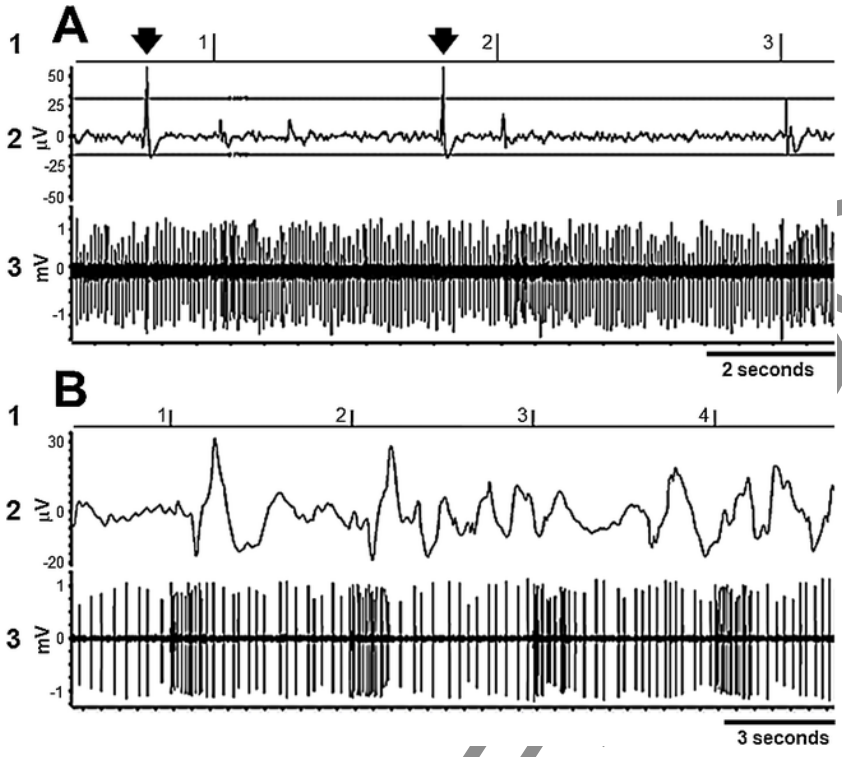

Fig. 3. Raw recordings showing the ERP suppression produced by the spontaneous (indicated by arrows) cortical activity (A) and by the presence of slow wave activity (B). In A and in B, 1 shows the signal of the RF stimulation, 2 shows ECoG activity, and 3 shows the recording of a single spinal cord neuron with RF. In A, notice the amplitude of ERP in the 3° stimulus and the reduction in 1 and 2, presumable produced by the previous ECoG activity. In B, notice the amplitude of the ERP in 1 and 2 and the reduction in 3 and 4 during the slow waves. In A, the frequency rate of RF stimulation was 0.2 cps and in B it was 0.5 cps. Notice that the ERP amplitude has no relation to the discharge frequency rate of the spinal cord neuron shown in A3 and B3. It is important to note that incoming spinal cord activity is not related with the amplitude changes in the ERP.

trode signals were amplified, filtered, digitized, and discriminated with CED hardware and Spike-2 software (Cambridge Electronic Design, Version 5.16). Waveforms of ECoG and recorded spike activities were stored on a computer disk for off-line analysis.

In the present study, we analyzed evoked responses in the ECoG produced by electrical stimulation of the RF. Therefore; we used only the control situations of the referred works in order to establish a possible relationship between the sensory input in spinal cord neurons and the magnitude of the evoked cortical potentials. No data included in this work were presented or published elsewhere. A new group of 7 rats was specifically prepared in similar conditions for ECoG and spinal cord neuronal activity. These rats enabled us to verify the effects of the interaction between the evoked cortical potentials (provoked by stimulation of the fore and lower limbs with different interstimulus intervals between them). In these cases, as in all the experiments, the ECoG and spinal cord activity coming from the lower limb receptive field activation were recorded, but in this series of experiments the ECoG presented the evoked activity for both fore and lower limb electrical activation. It is important to note that only one laminectomy was performed for recording the lower limb receptive field. In fact, the main point of this maneuver was to have two evoked activities with different intervals and compare their amplitudes like we did with the spontaneous potentials that affected the evoked responses.

Out of the 149 experimental rats, 62 were selected based on a recording frequency acquisition rate of more than 256 Hz. All the resampled experiments were down-sampled; we discarded all the experiments with a sampling less than 256 Hz and resampled all the experiments with higher sampling to that rate using a polyphase filter. This filter first upscales the signal by a factor of 10, subsequently filters the signal using a zero-phase low-pass FIR filter, and later downscales the signal by a factor of 10 times the ratio between the original signal and the signal at 256 Hz.

Data from all experiments were normalized to a mean of zero and a unit standard deviation to have a unique criterion for identifying activity peaks in the ECoG. For each experiment, the mean and standard deviation of the whole signal were computed and the data were transformed by subtracting the mean and dividing by the variance (z-standardization) so that the data of all the experiments conformed to the same distribution with a mean of zero and a standard deviation of one. This allowed us to have a unique criterion for identifying activity peaks in the ECoG.

This procedure homogenizes all the experiments and enables us to compare the experimental ECoG signals.

From each experiment, a series of 20-recorded events obtained in response to electrical stimulation of the receptive field were used (see recording procedures). Each event was extracted from the experiments by defining a window 1500 ms previous to the electric stimulation of the RF and a post-stimulus window of 500 ms after stimulation. The post-stimulus window used in the study was reduced by eliminating the first 35 ms to account for a latency period in the ECoG response and to avoid artifacts produced by electrical stimulation.

The post-stimulus window allows us to classify the event related potential (ERP) into three groups taking into account their amplitude: the POSITIVE events were those for which an ERP was present in response to the RF stimulation with no pre-event peak (see Fig. 4A1); the NEGATIVE events were those for which no ERP was present with a pre-event peak (Fig. 4B1); and the INTERMEDIATE events were those for both an ERP and pre-event peaks were present (Fig. 4C1). The analyses were divided according to the time of occurrence of the pre-event peak, and only the peaks that occurred 1500 ms before the stimulus were considered. These peaks were divided into periods as follows: events that occurred 1500 ms to 1000 ms before the stimulus, events that occurred between 1000 and 500 ms before the stimulus, and events that occurred 500 ms before the stimulus. This classification allows us to de-

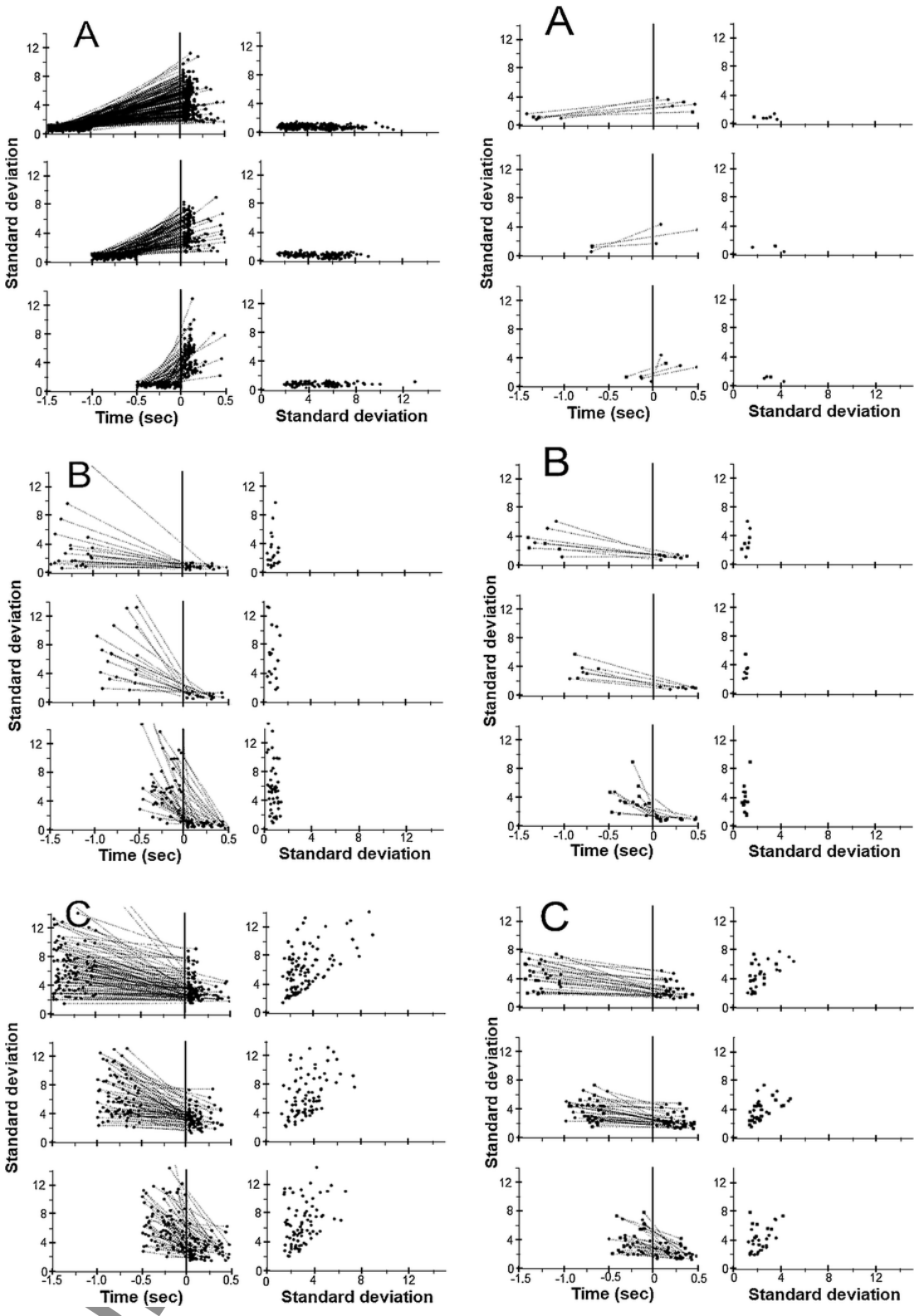

Fig. 4. Plots of the automatic detection of the three classes of events: POSITIVE (A), when the ERP was present; NEGATIVE (B), when the ERP was blocked by the presence of spontaneous activity in the cortex; and INTERMEDIATE (C), when both spontaneous activity and the ERP were present. Column 1 plots the data obtained with only the specific RF stimulation and column 2 presents the responses during the heterotopic stimulation of specific RFs in the lower limb and the stimulation in the upper limb. The left side of columns 1 and 2 represent the pre- and post-event peaks in time (from 1500 ms before the event to 500 ms after). A dashed line connects the values of the pair of peaks for each individual event. The right side of the plot represents the joint distribution of the standard deviation values of the peaks.In A1, B1, and C1 the upper graph shows the events before 1500 to 1000 msec, the graph in the middle is for the events in the window between 1000 to 500 msec, and the lower graph is for the events between 500 msec and the time of RF stimulation (see METHODS section). Notice that when the events were less than 2 Standard Deviations, the ERP were present (A1), but if the events preceding RF stimulation were higher than 2 SD an important reduction in the ERP were observed. In addition, a considerable amount of ECoG events with more than 2 SD did not modify the ERP (C1). The abscissas in the left columns in 1 and 2 have time

from −1.5 s before the RF stimulation at time 0 and 0.5 s after the RF stimulation. The ordinates for all the graphs show the amplitudes in SD from the EEG basal activity. The right columns in 1 and 2 display the SD of previous ECoG activity to RF stimulation in the ordinates and the SD of the amplitude of the ECOGr in the abscissas.

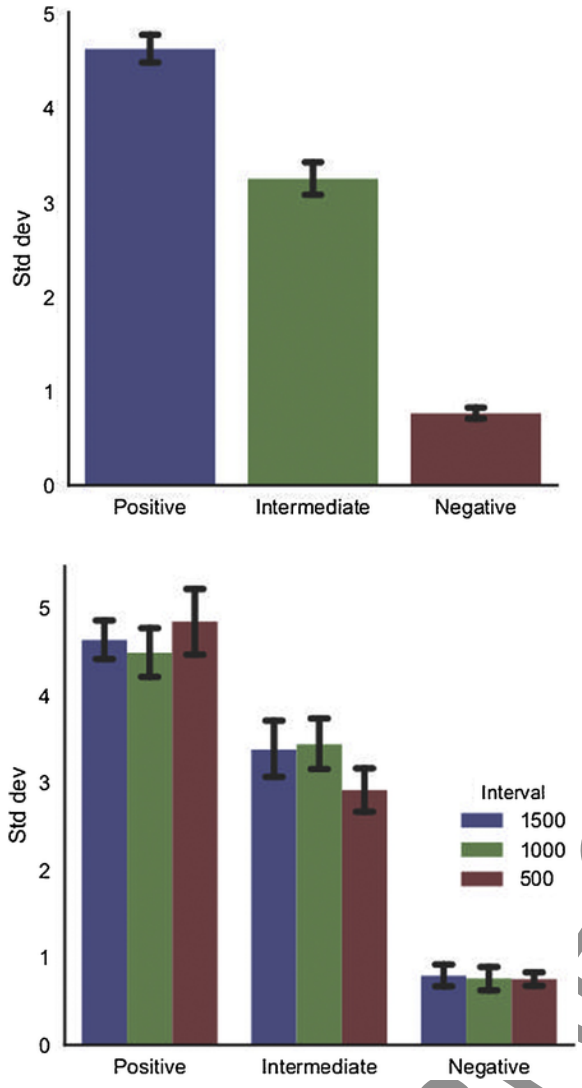

Fig. 5. Histograms of the mean amplitude and standard deviation of POSITIVE, INTERMEDIATE and NEGATIVE ERP. In the lower row the mean amplitudes are presented in relation to the three temporal windows (1500 to 1000, 1000 to 500 and 500 to RF stimulus). The comparison between POSITIVE vs INTERMEDIATE or NEGATIVE events is significant at level of < 0.001.

tect time differences related to the pre-event peak with the evoked potential amplitude values.

The criterion established to detect the existence of a pre-event peak was defined using a threshold of 1.5 standard deviations above or below the signal average. In other words, a peak was considered if the maximum of the signal inside a window exceeded 1.5 standard deviations over the mean. Next, the value for the threshold was 1.5 standard deviations and was automatically applied. However, this criterion was defined visually according to the average noise observed in the signal of the experiments.

2.2. Statistical analysis

A comparison between the distribution of maximum values of the peaks post-event was performed. The comparison was made between POSITIVE vs NEGATIVE or POSITIVE vs INTERMEDIATE events in the intervals of 1500-1000, 1000-500 and 500-0. A two-sided Kolmogorov-Smirnov (K-S) test was computed to determine if their individual distributions come from the same original distribution. Additionally, a two-sided K-S test was used to compare the frequency rate of single unit activity between POSITIVE vs NEGATIVE and POSITIVE vs INTERMEDIATE events.

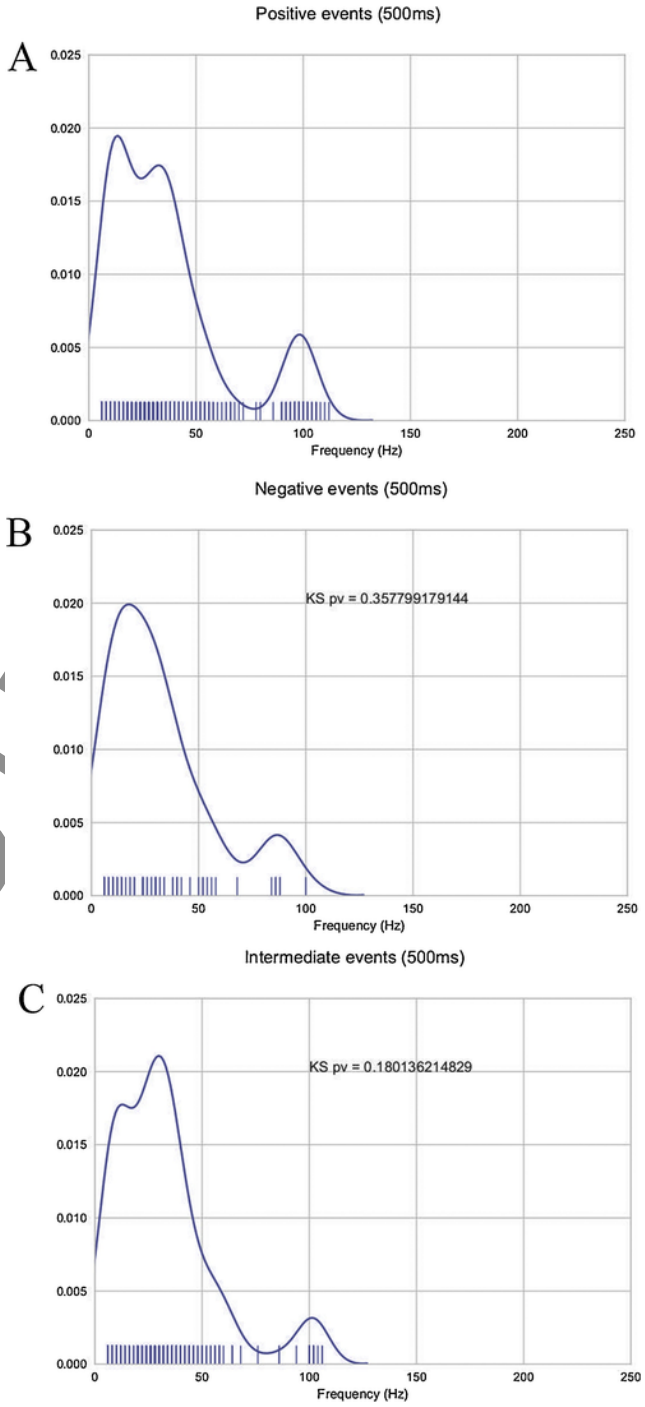

Fig. 6. Distribution of the discharge frequency of spinal cord neuron responses to nociceptive stimulation of RF. A) shows the values for the POSITIVE events, B) shows the distribution for the NEGATIVE events, and C) for the INTERMEDIATE events. The statistical comparison between POSITIVE and NEGATIVE or INTERMEDIATE were non-significant. Notice that the inputs to the spinal cord were similar in all the situations.

2.3. Histological controls

At the end of the experiments, the recording sites were marked by electrophoretic deposition of pontamine sky blue, and the position of the stainless-steel tip in the PVN was marked by an electrolytic lesion made with direct current. The lumbar spinal cord and the brains were removed and fixed by immersion in a 10% formaldehyde solution for 72 h and later soaked in a 30% buffered sucrose solution for 48 h. Samples were frozen, cut into serial 40-μm sections, and Nissl-stained with cresyl violet. PVN electrolytic lesions were reconstructed from camera lucida drawings of serial sections.

3. Results

Electrical stimulation of the hypothalamic paraventricular nucleus of the hypothalamus reduced activity of A-Delta and C-nerve fibers, as well as, reduced the post-discharge of primary afferent fibers arriving at the spinal dorsal horn wide dynamic range (WDR) neurons, as has been shown elsewhere [8,12,13,18]. The averaged events related potentials (ERPs) associated with nociceptive electrical stimulation are also temporally reduced, as Fig. 1A and B illustrates. Moreover, electrolytic lesions of the nucleus raphe magnus increased the evoked ERPs due to the elimination of the suppressive effect of the raphe magnus nuclei. This result is also illustrated in Figs. 1 and 2A and B. With frequencies of 0.2, 0.5, 1 and 2 Hz to nociceptive stimulation of the receptive field; the ERPs amplitude is decreased as the frequency rate increased (Figs. 1 and 2). The ECoG recording allowed us to observe the evoked potential related to electrical nociceptive stimulation of the left forepaw and lower paw, and in this situation, we performed paired stimulations. The ERP provoked by the forepaw and lower paw electric stimulation did not have the same amplitude, but when we reduced the interval between stimulations, the second response from the paired stimulus was reduced. Intervals of 1.0 s reduced the second evoked response, and intervals of 200 msec between the paired stimuli produced a total suppression of the second response. These results are illustrated in Figs. 2 and 3.

During the ECoG recordings, we observed that when a spontaneous, high-voltage activity was presented before the expected evoked potential in response to RF stimulation, the response was reduced. Moreover, during a period of high-voltage slow wave activity, the presumed responses were also blocked. However, the simultaneous recording of single unit activity in the spinal cord dorsal horn neurons showed that the incoming afferent activity provoked by RF stimulation remained unaltered. These data suggest that the input is present at the spinal cord level, but the cortical response is subject to another supra-segmental control. These results are illustrated in Fig. 3A and B.

With these preliminary observations, we decided to use an automatic procedure to detect high-amplitude signals in the ECoG before electrical stimulation of the RF. We also sought to establish a correlation between the incoming sensory activity, measured as the frequency of spinal cord cell discharge, and the amplitude of the ERP. As described in the Methods section, we set a fixed detection threshold of 1.5 Standard Deviations (SD) above or below the spontaneous ECoG activity to detect an electrographic event, which was later correlated with the ERP produced by RF nociceptive stimulation. Using this criterion, we learned that out of a total of 924 RF stimulations, 579 were POSITIVE when the preceding activity did not alter the ERP (Fig. 4A1), 89 were NEGATIVE when the preceding activity had more than 2.5 SD and suppressed the ERP (Fig. 4B1), and 256 were INTERMEDIATE when the preceding ECoG activity had more than 2.5 SD and the ERP remained (Fig. 4C1). In the left column of Fig. 4, the POSITIVE results are illustrated in A, NEGATIVE in B, and INTERMEDIATE in C. In other words, the amplitude of the ERP was drastically reduced (below the 1.5 SD threshold) when a preceding event was detected for the NEGATIVE events, but also, a significant reduction in the ERP was observed in the presence of INTERMEDIATE events. Nevertheless, the ERP during the INTERMEDIATE events was higher than the threshold of 1.5 standard deviations. The aforementioned reductions were observed in the three preceding temporal windows of 1500 to 1000, 1000 to 500 and 500 to the time of RF stimulation. These results are shown in Fig. 5. In order to compare the values of the peaks in these three cases we performed a one-way ANOVA to check if their distributions had the same mean, with a resulting p-value of 4.5e-10. A post-hoc analysis using Tukey's HSD test with alpha = 0.05 confirmed that all the means were different among them. We also compared the means of the values of the peaks for each case separately for the three temporal windows mentioned before performing three ANOVA tests. For the POSITIVE events the p-value of the test was 0.34, so the means were not different. For the NEGATIVE events the p-value of the test was 0.89, so the means were not different either. For the INTERMEDIATE events the p-value of the test was 0.03, so we proceeded with the post-hoc test using Tukey's HSD test. In this case, the result was that the mean value of the events in the window 500 to 0 was different from the other two intervals.

3.1. Correlation between the evoked amplitude of ERP and the frequency rate of single units recorded in the spinal cord

Out of a total of 864 neuronal responses in the spinal cord (evoked by electrical stimulation of the RF), 530 were classified as POSITIVE, 68 were classified as NEGATIVE, and 236 were classified as INTERMEDIATE. The frequency rate (number of spikes per unit time) during the 500 ms of the post-event window was determined and the main response activation of the spikes generated by the nociceptive stimulus were compared as follows: the spikes generated during the POSITIVE events were used as a reference (i.e., as a control value) and were compared with the other two NEGATIVE and INTERMEDIATE classes.

A two-sided Kolmogorov–Smirnov (K–S) test was performed to determine if the distribution of spike frequencies for the NEGATIVE and INTERMEDIATE events was generated from the same distribution as the POSITIVE events. The K–S test had a p-value of 0.35 for the NEGATIVE events and a p-value of 0.18 for the INTERMEDIATE events. Therefore, in all cases the distributions were the same, meaning that the input conditions (considered as the number of action potentials in the recorded spinal cord cells) for all experiments were equivalent. Also, considering that we were performing multiple tests, we performed a Bonferroni correction for the significance of the p-value. In this case all the p-values were not significant, and the single units recorded during the different conditions were similar.

These results are illustrated in Fig. 6.

4. Discussion

The primary results are as follows: the ERP obtained in response to RF nociceptive stimulation is related to the inhibitory action of PVN stimulation, as well as to the lesions of inhibitory structures, such as the RMg. There is an important relationship between the amplitude of ERP and the preceding spontaneous or evoked ECoG activity. The significant relationship between the previous high ECoG activity and the reduction in the ERP is not correlated with the sensory input, which is evaluated as the frequency rate of spinal dorsal horn neurons in response to the same noxious stimulus. The reduction in the ERP was observed during the frequency stimulation (Figs. 1 and 2) of 0.5, 1, and 2 cps when the responses were compared with those obtained at a frequency rate of 0.2 cps. Interestingly, when we used heterotopic stimulation with electric paired pulses at the fore and lower limbs and the interval between stimulations was less than 1 s, we observed a reduc-

tion in the second response, which reached the total diminution of the second ERP when the interval was between 1000 msec and 200 msec. These results are in agreement with our hypothesis that a cortico-cortical inhibitory control is responsible for the reduction in the second responses.

The ECoG activity recorded in our experiments originates from a wide region of the sensory-motor cortex, which enabled us to both delineate an extended portion of the cortex and record the ERP related to nociceptive stimulus in both the upper and lower arms due to their close cortical representation.

The most interesting element of our results is that the amplitude of the ERP is not related to the sensory input at the spinal cord level. There were a total of 924 (100%) ERP, out of which 574 (62%) were POSITIVE, 89 (10%) were NEGATIVE, and 256 (27%) were INTERMEDIATE. The NEGATIVE responses had an amplitude below the 1.5 standard deviation cutoff for basal activity, and the INTERMEDIATE responses were significantly smaller than the POSITIVE responses.

Approximately 37% of the ERP were affected by preceding activity. In these circumstances, the real value of the ERP needs to consider the previous background activity in order to generate an accurate interpretation. We believe that the described cortical effect has a local action throughout the inhibitory cortical cytoarchitecture, as was postulated for the specific cortical representation [20]. However, the facilitator cortical action upon both specific and nonspecific thalamic nuclei could be absent during and after the previous periods of high-amplitude activity in the cortex, giving rise to a lack of facilitation at the thalamic level and thereby blocking the incoming sensory activity [12,19–21]. Interestingly, electrical stimulation of nonspecific thalamic nuclei, such as the intralaminar thalamic nuclei, generates antidromic activity in cortical neurons. These responses follow patterns of high-frequency stimulation. In contrast, electrical stimulation of specific thalamic nuclei, such as the ventral posterolateral nucleus, leads to following of only the first stimulus when a high frequency stimulus is used; suggesting that a recurrent inhibitory action affects antidromically activated cortical neurons [19,22].

It is difficult to determine if the ERP diminution is due to a specific cortical action, as our results seem to suggest, or if cortico-thalamic interactions and the cortico-spinal pathway are also potentially involved. In this regard, it has been demonstrated that electrical stimulation of the sensorimotor cortex produces primary afferent depolarization in both cutaneous and primary motor afferent fibers [23–25].

In any case, the current results suggest a method consisting of normalization and analysis of ECoG activity in the time window before the ERP, evoked potentials, or potentials related to other events in order to have more consistency in the results and conclusions. Another interesting point of view is to examine the possible action of the evoked activity in the cerebral cortex using transcranial direct current stimulation or magnetic cortical stimulation to generate activity capable of suppressing the incoming sensory activity, thereby yielding potential non-invasive mechanisms for pain amelioration in central neuropathic pain [26]. Finally, Figs. 5 and 6 show that the incoming activation at spinal cord level did not change, but the ERP did, possibly due to supraspinal control actions over the incoming activities. We were describing that we are talking about a cortico-cortical control system.

5. Conclusions

The electrocortical activity is a main source to evaluate the general state of central nervous system, the integrity of main cognitive functions and to measure the sensory perception by the evoked or related activities to sensory stimulation. We observed that the previous ECoG activity to a given noxious stimulation could change the amplitude of ERP and then the integrative function of the sensory input. The main result is that no correlation between the sensory incoming activities measured at the spinal cord level neuronal discharge and the amplitude of the ERP was always direct. It is required to take in account the previous activity to a sensory stimulation in order to evaluate sensory perceptions. A cortico - cortical inhibitory system is proposed that could participate in the effects of transcranial electric or magnetic stimulation.

Uncited References

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