Cortical modulation of dorsal column nuclei: A computational study

Eduardo Sánchez , Senén Barro, Jorge Mariño, Antonio Canedo

Abstract

We present a computational study aimed at exploring the sensorimotor cortex modulation of the behaviour of dorsal column nuclei, specifically the impact of synaptic parameters, during both sleep and waking conditions. On the basis of the circuit proposed by Canedo et al. (2000), we have developed realistic computational models that have been tested with simultaneous electrocorticographic as well as intracellular cuneate recordings performed in anaesthetized cats. The results show that, (1) under sleep conditions, the model can block the transmission of afferent sensory information and, (2) operations expected during wakefulness, such as filtering and facilitation, can be performed if synaptic parameters are appropriately tuned.

1. Introduction

The dorsal column nuclei (DCN), located in the most caudal area of the brainstem, are constituted by the gracile (GN) and the cuneate (CN) nuclei. Both nuclei have a similar topographic organization (neuronal types and connections), differing in the origin of their primary afferents: GN neurons receive inputs from lower thoracic and lumbar segments, while CN inputs arise from the upper part of the trunk and forelimbs.

The DCN constitutes a part of the dorsal column-medial lemniscus (DC-ML) pathway, which processes cutaneous and proprioceptive information. This pathway is constituted by peripheral receptors, the aforementioned DCN, the ventro-postero-lateral (VPL) nucleus of the thalamus, and the somatosensory cortex (SSC); connected through several bundles of ascending fibers: primary afferents, fibers forming the medial lemniscus (ML) (which connect the DCN with the VPL), and thalamo-cortical axons. This pathway is modulated by a large number of descending fibers from the sensorimotor cortex (SMC), contacting topographically related areas of subcortical structures (Bindman and Lippold, 1981 ; Kuypers, 1981 ; Canedo, 1997).

- SMC fibers to the VPL. Arising in layer VI of the SMC and making synaptic contacts with thalamocortical (TC) neurons and local internerneurons, as well as with the GABAergic cells of the thalamic reticular nucleus (TRN).
- SMC fibers to the DCN. Grouped into two main tracts (Canedo, 1997 ; Bindman and Lippold, 1981): direct corticocuneate fibers and collaterals of the corticospinal tract. The former have their origin mostly in areas 1, 2 and 3b of primary somatosensory cortex. The latter, which do not send collaterals to the VPL or to the TRN (Castman-Berrevoets and Kuypers, 1976), are constituted by axons arising from area 4 (primary motor cortex (MC)), area 6 (premotor cortex), and areas 1, 2 and 3 (SSC) (Biedenbach and De Vito, 1980). These tracts also differ in their conduction speeds, which are slower for the corticocuneate fibers (Lamas et al., 1994 ; Martinez et al., 1995).

1.1. The cuneate nucleus and the corticocuneate circuitry

The middle zone of the cuneate nucleus (CN), located be- tween the obex and 4 mm caudal to it. This area is composed of a core or central region, and a shell or peripheral region. The core is basically made up of clusters of cuneothalamic (CT) neurons (Kuypers and Tuerk, 1964), also referred to as projection or relay neurons, which are surrounded by interneurons, also known as local neurons or non-thalamic

projection neurons. The shell, comprising the ventral and marginal regions, is mostly made up of interneurons. CT cells project their axons to the VPL nucleus whereas interneurons exert their influence on CT neurons as well as other interneurons.

The CN receives inputs from primary afferents (originating from cutaneous and deep receptors), brainstem, and SMC. Cutaneous fibers are basically confined to the central region of the middle cuneate nucleus, preferentially establishing axodendritic synapses (Fyffe et al., 1986). Primary afferents carrying proprioceptive information make synaptic contacts within the shell. Finally, the descending direct and corticospinal collateral branches can be grouped on the basis of their cortical origin: those originating in Brodmann's areas 4 (MC) and 3a (proprioceptive SSC) contact the shell (Cheema et al., 1984 ; Martinez et al., 1995); those from area 3b (cutaneous SSC) project directly to the core; and those from areas 1 and 2 (cutaneous SSC) project directly into the shell as well as into the core but within zones surrounding the cluster of CT cells.

The effects of cortical descending fibers on DCN cells have previously been studied by Jabbur and Towe (1961), Towe and Jabbur (1961), and Levitt et al. (1964). These re- searchers found that SMC either excites, blocks or has no effect on the activity of DCN cells. Gordon and Jukes (1964) reported that cortical stimulation inhibits neurons in the me- dial DCN region. This inhibition was partially explained by the depolarization of primary afferent cutaneous terminals (Andersen et al., 1964a, b). Corticofugal fibers would excite DCN interneurons, which in turn would depolarize the primary afferent terminals and thus decrease the synaptic effect of sensory signals. The overall effect would be presynaptic inhibition. On the other hand, it was also demonstrated that SMC could directly excite CT cells (Darian-Smith, 1966 ; Winter, 1965). Recent experiments in the cuneate nucleus, based on intracellular recordings in vivo (Mariño et al., 1999 , 2000 ; Canedo et al., 2000) have confirmed the results of some of the classical studies, have questioned others and have added new insights about synaptic connections and relationships between the cerebral cortex and the CN. With regard to cuneate interneurons, in addition to excitatory effects, cortical inhibitory effects have also been observed (Canedo et al., 2000). Moreover, excitation and inhibition on the same interneuron have been discovered (Canedo et al., 2000)after stimulating SSC and MC, respectively. Regarding CT neurons, both inhibitory (Mariño et al., 1999) and excitatory effects (Mari˜ no et al., 2000) were confirmed. How- ever, the mediating inhibitory mechanism is still open to de- bate as recent data provides evidence of postsynaptic rather than presynaptic inhibition (Canedo, 1997 ; Aguilar et al., 2003). All these findings suggest the existence of a complex corticocuneate circuitry (Canedo et al., 2000), as shown in Fig. 1 .
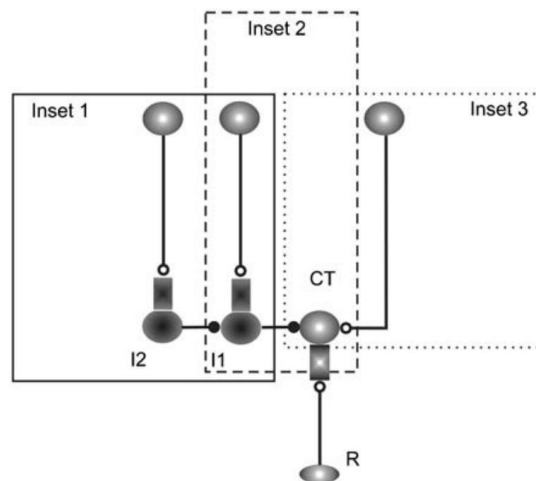

Fig. 1. The corticocuneate circuitry. Three possible synaptic connections are depicted: cortical excitation and inhibition on interneurons (inset 1), cortical inhibition on cuneothalamic neurons (inset 2), and cortical excitation on cuneothalamic neurons (inset 3). Scheme adapted from Canedo et al. (2000)

Our interest is focused on the role of corticocuneate circuitry during wakefulness and sleep. It has been proposed that, during wakefulness, SMC could control the flow of information through the DCN by two complementary mechanisms (Mountcastle and Darian-Smith, 1968 ; Canedo et al., 2000): (1) facilitation of the transmission of information originating in those cutaneous areas that either process a high intensity stimulus or are inside the window of cortical attention; and (2) filtering of irrelevant information. Recent findings have also shown that during sleep, descending cortical fibers play an important role by imposing oscillatory rhythms on the DCN (Mari˜ no et al., 1996 , 1999). These rhythms, which have been intensively studied in the thalamus (McCormick and Bal, 1997 ; Steriade et al., 1993), are assumed to be in charge of blocking the ascending inputs at subcortical stages.

The aim of the present study was to analyze the behaviour of the circuit proposed by Canedo et al. (2000) under different synaptic configurations, and particularly, to find out which synaptic parameters explain the behaviour observed in vivo in sleep as well as wakefulness. We present: (1) the computational methods used in the present study, (2) a computational model for the circuitry proposed by Canedo et al. (2000), (3) computer experiments performed with the model, and predictions derived from them, and (4) a final discussion. 2. Methods 2.1. Neuronal and membrane level Neurons were modeled using a multi-compartmental approach (Rall, 1964). The membrane potential for each compartment is described by:

$$
C \frac{\partial V}{\partial t} = -I_\mathrm{m} - I_\mathrm{syn} - I_\mathrm{inject} - \frac{(V' - V)}{R'_\mathrm{a}} - \frac{(V'' - V)}{R''_\mathrm{a}}
$$

where C is the membrane capacitance, I_m the sum of the ionic currents, I_{syn} the synaptic current, I_{inject} the electrical stimulation, R a the axial resistance, and ($V' - V$)/ R'_a and ($V'' - V$)/ R''_a a denote the axial currents between each compartment and the adjacent ones.

As regards the membrane level, all the ionic currents were described by the Hodgkin-Huxley model (Hodgkin et al., 1952).

The model consists of different types of neurons, compartments and ionic currents.

1. Cuneothalamic cells. Composed of three compartments: one soma and two dendritic branches. In the soma, the most important ionic channels were a high-threshold calcium current I_L , a calcium-activated potassium current I_{ahp} , a hyperpolarization-activated cationic current I_h , and a low-threshold calcium current I_T .The mathematical description of these currents can be found in Sánchez et al. (2003). In dendrites, we have used a simple fast sodium current (Huguenard et al., 1988) and a delayed rectifier potassium current (McCormick and Huguenard, 1992).
2. Interneurons. Composed of three compartments for soma, axon and dendritic trees. In the soma, the ionic currents were similar to those at the soma of CT cells with two major differences (Sánchez et al., 1998): (1) a slow potassium current I_A (Huguenard et al., 1991), and (2) the substitution of I_{ahp} by a different calcium-dependent potassium current I_C (Yamada et al., 1989). In dendrites, we have used the same fast sodium current and delayed rectifier potassium current as in cuneothalamic cells.
3. Primary afferents and cortical neurons. Two compartments for soma and axon. We took the membrane current as the sum of a fast sodium current (Huguenard et al., 1988), and a delayed rectifier potassium current (McCormick and Huguenard, 1992).

2.2. Synaptic level

To describe conductance dynamics associated with the synaptic current we have used the alpha function, which represents the conductance associated with the synaptic current and determines the shape of the postsynaptic potential generated after appropriate stimulation (Jack and Redman, 1971). Its mathematical expression is:

$$
g_\mathrm{syn}(t) = \alpha \frac{t - t'}{\tau} e^{\frac{t-t'-\tau}{\tau}}
$$

where α is a constant, t the initial time, and τ the time constant. The synaptic conductance will equal the alpha function if the presynaptic potential is greater than a certain threshold, and zero otherwise. The

threshold represents the membrane potential required to activate the release of neurotransmitter needed to activate the postsynaptic receptors.

The conductance g_{syn} determines both kinetics and amount of the synaptic current I_{syn}:

$$I_{syn}(t) = g_{syn}(t)(V - V_{syn})$$

where V_{syn} denotes the resting potential of the postsynaptic membrane. In the model we introduced both excitatory and inhibitory connections. We assumed the latter to be GABAergic and the former glutamatergic. Excitatory connections were modeled by setting V_{syn} to zero and the inhibitory connections to a negative value.

2.3. Simulation tools

For the simulations we used Neuron (Hines, 1989), as it provides an optimized integration method, which combines the advantages of Crank-Nicholson and Euler methods. The computer used for the simulations was a PC with a 1 Ghz AMD Athlon processor.

3. Results

In this Section we explain how we modeled the circuit pro- posed by Canedo et al. (2000) and shown in Fig. 1 .The neurons are realistic computational models (Sánchez et al., 1998 , 1999 , 2003) based on data from current injection experiments (Canedo, 1997 ; Canedo et al., 1998). The models were validated against neuronal activity recorded in vivo in anaesthetized cats.

3.1. Modelling the corticocuneate circuitry

The corticocuneate connections were modeled on the ba- sis of data extracted from Mariño et al. (1999, 2000), and Canedo et al. (2000). The corresponding experiments were performed in intact-brain preparations in anaesthetized cats. The SMC was electrically stimulated at 1–10 Hz, and simultaneous recordings both in SMC and CN were obtained. At the CN, intracellular recordings permitted the study of the effects induced by SMC stimulation. In the following sub- sections we present a comparison between the experimental evidence and the simulations obtained from the computational model.

3.1.1. Cortical influence on interneurons

Three main cortical effects on cuneate interneurons were considered:

- Excitation. 1–10 Hz electrical stimulation of SMC can induce monosynaptic excitatory responses on cuneate interneurons (Fig. 2 A-1). We have simulated the presumed underlying microcircuit (Fig. 2 A-2), stimulating a simplified cortical neuron with 1 nA current, and comparing the simulated behaviour with the experimental behaviour. The synaptic reversal potential was set to characterize a common excitatory synapse ($V_{syn} = 0$ mV), and the synaptic parameters were adjusted to reproduce the observed in vivo behaviour, thus setting a small maximum conductance $g_{syn}^{max} = 0.01$ mS, and a high time constant $\tau = 10$ ms. As a result, the interneuron I1 responded generating some spikes (Fig. 2 A-3).
- Inhibition. Interneurons can also be inhibited by 1— 10 Hz electrical stimulation of SMC (Fig. 2 B-1). The suggested circuitry (Fig. 2 B-2) involves two interneurons: I2, excited by the cortex, and I1, which is inhibited by I2. In our simulations, a cortical neuron was stimulated by injection of 1 nA current during 10 ms and again the synaptic parameters were adjusted to reproduce the experimentally observed behaviour. The connection be- tween sensorimotor cortex and I2 was characterized with g max syn = 0 . 01 mS, $\tau = 2$ ms, and V syn = 0 mV; and the connection between I2 and I1 with: $g_{syn}^{max} = 0.03$ mS, $\tau = 3$ ms, and $V_{syn} = -70$ mV. A simulation of I1 with membrane hyperpolarization after cortical stimulation is shown in Fig. 2 B-3.
- Excitation and inhibition on the same interneuron. This effect was shown after stimulating both MC and SSC. MC elicits inhibitory responses whereas SSC elicits subthreshold excitatory ones. A circuit providing an explanation for these findings is illustrated in Fig. 2 C-2, and is consistent with the cortical effects discussed so far in this section. Simulation results, shown in Fig. 2 C-3, were achieved

with the synaptic parameters described above, but with a smaller stimulation current intensity (0.5 nA) intended to generate subthreshold responses.
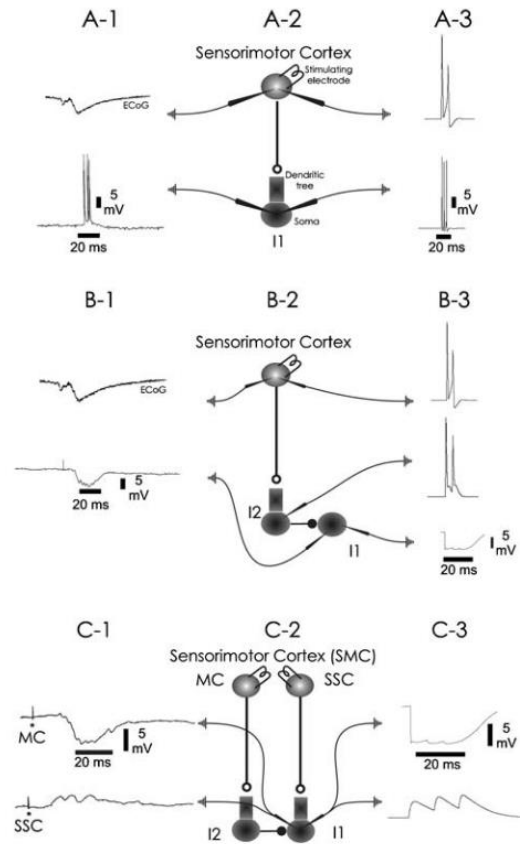

Fig. 2. Cortical-induced effects on interneurons. Electrical stimulation of the sensorimotor cortex (SMC, upper records of A-1 and B-1), have shown the following cortical effects on cuneate interneurons: (1) excitation (lower record of A-1; traces from Mariño et al. (2000)); (2) inhibition (lower record of B-1; traces from Canedo et al. (2000); and (3) both inhibition from MC (upper record of C-1), and excitation from SSC (lower record of C-1; traces from Canedo et al. (2000)). The circuits provide an explanation for these effects (A-2, B-2 and C-2). Simulations with a realistic computer model reproduced the experimental results after adjusting the synaptic parameters (A-3, B-3 and C-3)

3.1.2. Cortical influence on cuneothalamic neurons
Two major effects on CT neurons were considered:

- Inhibition. Cortical stimulation can induce hyperpolarization of the CT neuron followed by a post-inhibitory excitatory rebound (Fig. 3 A). This finding is explained by postsynaptic inhibition. Synaptic parameters for the interneuron-CT neuron connection ($g_{syn}^{max} = 0.3$ mS, $\tau = 5$ ms, and $V_{syn} = -90$ mV) were found to achieve the hyperpolarization required to activate hyperpolarization- dependent cationic currents, I_h , and de-inactivate the low- threshold calcium current, I_T . When the inhibition ceases, I_T depolarizes the membrane and triggers a burst of spikes (Fig. 3 C).
- Excitation. This phenomenon has been confirmed by Mariño et al. (1999), and can be explained by means of descending cortical fibers establishing direct excitatory synapses on CT neurons. Synaptic connections were simulated with $g_{syn}^{max} = 0.1$ mS, $\tau = 2$ ms, and $V_{syn} = 0$mV, to achieve the results shown in Fig. 4 (1 nA electrical stimulation of the sensorimotor cortex).
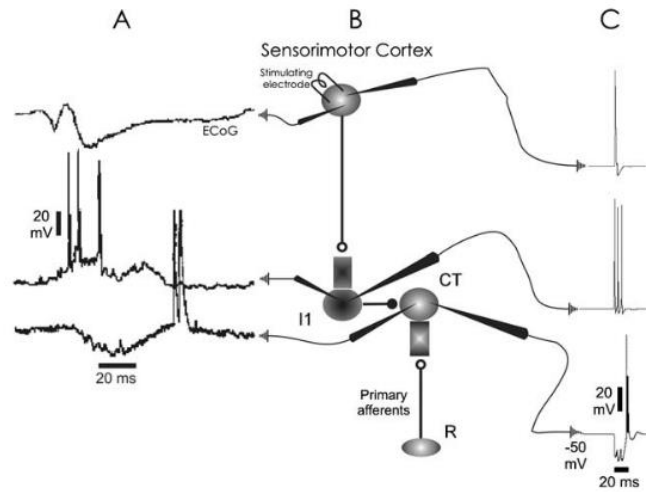
Fig. 3. Cortical-induced inhibition on cuneothalamic neurons. Stimulation of SSC (upper record of inset A) elicits inhibition of CT neurons, followed by a depolarizing rebound (lower record of inset A; traces from Mariño et al. (1999)). The circuit explains the hypothesized underlying mechanisms (B). Simulations were performed adjusting the synaptic model to reproduce the observed behaviour (C)
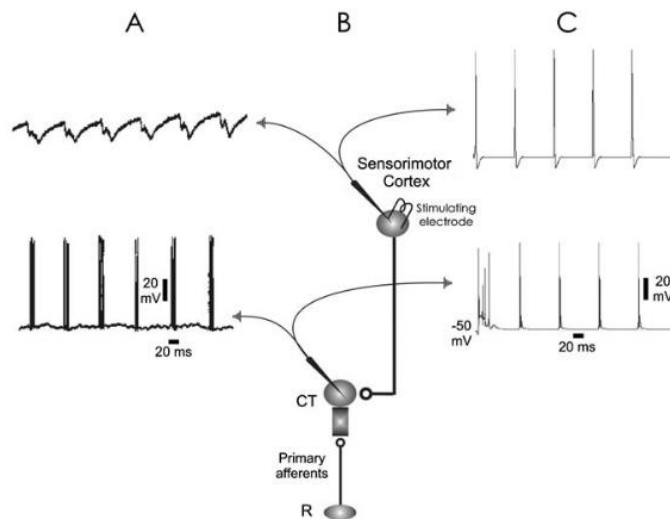

Fig. 4. Cortical-induced excitation on cuneothalamic neurons. Stimulation of SMC (upper record of inset A) can also elicit excitation on cuneothalamic neurons (lower record of inset A; traces from Mariño et al. (2000)). A simple circuit can explain the results (B). Simulations reproduce the pattern observed experimentally (C)

3.2. Prediction

The synapses of the computational model described so far were adjusted by comparing simulated outcomes with experimental neuronal activity recorded in anaesthetized cats. The model is therefore tuned to sleep state conditions. At this point we posed the following questions: (1) Can the model perform the blocking of the transmission of sensory information, as is expected to occur during sleep? (2) Can the same model operate in waking conditions as is expected, i.e. performing filtering and facilitation, as proposed by Mount- castle and Darian-Smith (1968) and widely accepted in the literature?.

3.2.1. Sleep state

The model was used to test whether the corticocuneate circuitry under sleep conditions can block ascending sensory information. A CT neuron being inhibited by cortical stimulation (same parameters as discussed in Section 3.1) is shown in Fig. 5 . The hyperpolarization activates I_h and de- inactivates I_T, which leads to bursting activity initiating a spindle-like rhythm. We activated a sensory receptor to generate primary afferent input. The sensory information did not alter the oscillatory pattern and hence the signal was completely blocked; at the hyperpolarization subcycle the firing threshold is so high that sensory signals can only drive a small membrane depolarization; at the depolarized subcycle, the intrinsic-generated spikes completely mask the processing of afferent signals. Therefore, the model supports the hypothesis of ascending information blockade by means of cortical-imposed oscillatory activity.
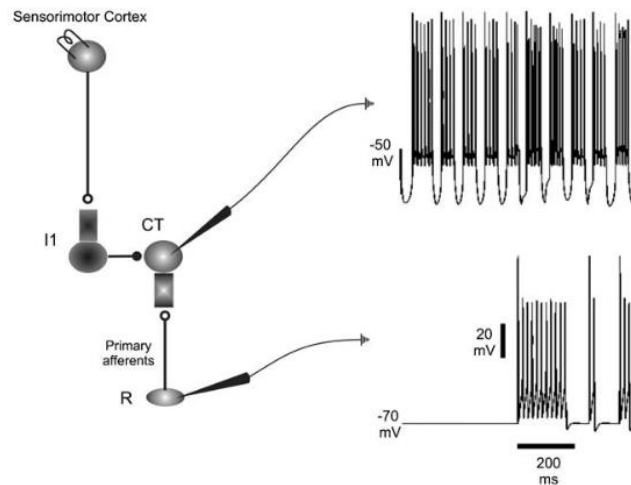

Fig. 5. Oscillatory activity and blockade of afferent information. The inhibition originated from SMC elicited an oscillatory bursting response on the CT neuron (upper right). From 400 to 800 ms, cutaneous stimulation was generated with different temporal durations (lower right), but the oscillatory activity prevented the transmission of this information

How does the complete circuitry work together? To investigate this we set up a simulation with the whole circuitry depicted in Fig. 6, in which the cortical neurons that elicit inhibition (CI) and excitation (CE) on CT neurons were stimulated. On the basis of the findings of Canedo et al. (2000) we also considered the CT-TC-CE pathway, which explains the transcortical effects observed after stimulating the Me- dial Lemniscus, and a connection between CE and cortical neurons that inhibit interneurons (CD). The results indicate that both depolarized and hyperpolarized subcycle periods last longer than the spontaneous activity shown in Fig. 5. The relatively long duration of the hyperpolarized subcycle occurred because we simulated a slow rhythm in the SMC, and thus the CT neurons are inhibited during a longer period of time. That of the depolarized subcycle is because of the excitatory cortical descending fibers providing excitation. In fact, we have found that this is the only mechanism of accomplishing an activity pattern similar to that observed *in vivo* (Mariño et al., 1999). We therefore predict that the ex- citatory connections play a fundamental role in the shaping of the slow rhythms in the DCN and determine the duration of the spiking subcycle.
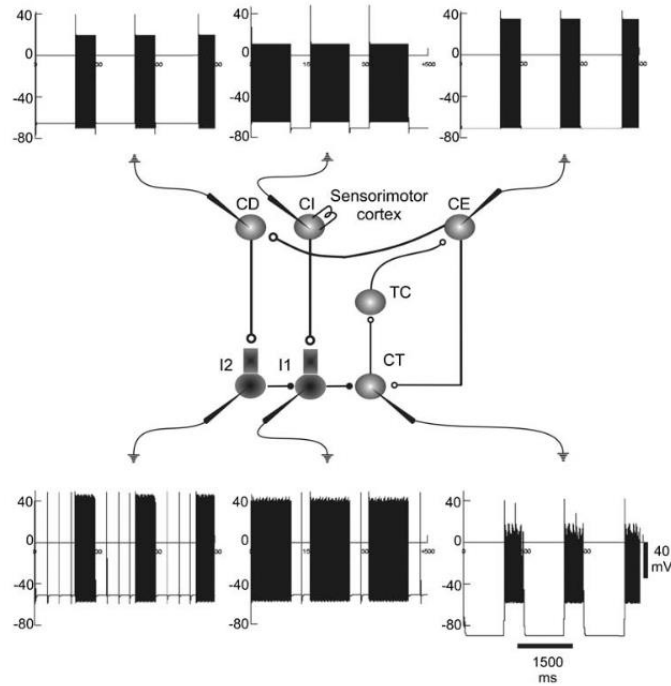
Fig. 6. Slow rhythms and the participation of excitatory synapses on their activity pattern. The circuit shown in Fig. 1 has been completed with the CT-TC-CE pathway and the CE-CD connection (see text for further details). A sensorimotor cortical neuron (CI) was stimulated to induce a slow rhythm (< 1Hz) that spread throughout the entire corticocuneate circuitry. As a result the CT neuron displayed an oscillatory activity very similar to that observed *in vivo*. The hyperpolarized subcycle was determined by the duration of inhibition carried out by I1. The depolarized bursting subcycle was determined by the duration of the cortical excitatory effects maintained through the CT-TC loop

3.2.2. Waking state

Considering Mountcastle's approach, SMC should influence DCN to perform two main tasks during wakefulness: filtering of irrelevant or unwanted information, and facilitation of relevant stimuli. To model this behaviour we first need to consider what wakefulness means. Or, in other words, what we should change in the model to satisfy the waking conditions. The activation of cholinergic and noradrenergic neurons in the brainstem produces prolonged depolarization of TC cells (Steriade et al., 1993). The underlying mechanisms involve, amongst other things, the activation of muscarinic receptors by acetylcholine, and α_1 -adrenoreceptors by noradrenaline, which reduce the activity of a K + conductance. In the cuneate nucleus, brain stem (Sotgiu and Margnelli, 1976) or cortical afferents (Martínez et al., 1995) may induce similar effects and be in charge of inducing the transition from sleep to wakefulness. We have simulated these effects by changing V_{syn} from –90 mV to –70 mV. In this way, we avoid the activation of I_h and I_T currents.

Firstly, we wished to test the filtering role of cortical inhibition on CT cells by means of simulating the basic circuitry shown in Figs. 3 and 5. The stimulation at 100 ms of 4 cutaneous receptors (R) establishing excitatory synapses (g_{syn}^{max} = 0.005 mS) with CT neurons generated action potentials at those neurons. We then stimulated the SMC, at 200 ms, which activated the cuneate interneuron I1, and then inhibited the CT neuron (maximum conductance g_{syn}^{max} = 0.3 mS, and time constant τ = 5 ms). The elicited inhibition raised the firing threshold and blocked the transmission of information. When the number of activated receptors was increased to 6 the input signal was strong enough to fully overcome the inhibition imposed by SMC, the threshold was therefore reached, and the CT neuron could follow the input without interruption. Finally, the activation of 10 receptors produced a more robust response, and the magnitude of post- spike repolarization was highly reduced. In summary, SMC could modify the firing threshold of CT cells by inhibiting those cells through local interneurons. The deeper the inhibition, the higher the firing threshold in CT neurons and, thus, the higher the required afferent input to overcome the inhibition.

The next step involved investigating the facilitation role of the excitatory connections between SMC and CT neurons. The CT neuron activity after setting the same synaptic parameters for excitatory cortical descending fibers as those found in Section 3.1.2 (g_{syn}^{max} = 0. mS, and τ = 2 ms), is shown in Fig. 7 A.

The following protocol for cutaneous stimulation was used:

- 0–100 ms. No stimulus.
- 100–200 ms. 3 receptors activated (synapses with $g_{syn}^{max} = 0.005$ mS).
- 200–400 ms. 6 receptors activated.
- 400–600 ms. 3 receptors activated.
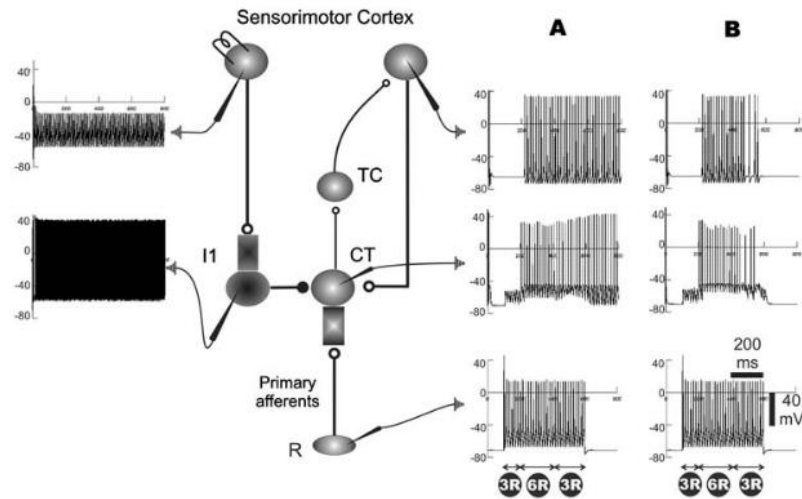- 600–800 ms. No stimulus.

Fig. 7. Cortical excitation of CT neurons and the mechanism of facilitation. High maximum conductance values and low time constants (A) determine a closed cuneate-thalamo-cortical loop when the cortical inhibition is overcome with the activation of 6 receptors. This circuitry facilitates firing of the CT neuron even when the number of activated receptors is reduced to 3. However, the neuron does not stop firing after the end of the stimulation. On the other hand, low maximum conductance values and high time constants (B) provide the same facilitation mechanism but the CT neuron does not generate any more spikes when the stimulation ceases

We observed that between 100 and 200 ms, stimulation with 3 receptors did not reach threshold. After activating 6 receptors, afferent signals did overcome the cortical inhibition and reach the sensorimotor cortex. The cortical neuron was then activated, sending excitatory feedback signals through the corticocuneate fibers. This new cuneate input was integrated with the afferent input to maintain the depolarization of the CT neuron. The depolarization was strong enough to allow previously subthreshold signals also to over- come the cortical inhibition. This phenomenon is illustrated in the interval from 400–600 ms, in which the number of activated receptors was reduced to 3. Although it elicited a subthreshold input during the 100–200 ms interval, during the 400–600 ms interval the signals elicited a response in the CT neuron due to the cortical excitatory effect. However, the most important observation is that the CT neuron generates spikes even after finalization of afferent stimulation, which means a disconnection between the CT neuron and the primary afferents. This disconnection is explained by considering that a closed loop is established between the cerebral cortex and the cuneate nucleus, which makes the latter independent from afferent stimulation. Although this may make sense as part of the blocking mechanism discussed for the sleep state, it seems clear that the simulated excitatory mechanism cannot play any facilitatory role.

At this point, we need to address the issue of what is the appropriate synaptic configuration to obtain such facilitation. We have followed a qualitative approach in which we identify four different synaptic configurations after set- ting high and low values for both maximum conductance g_{syn}^{max} and time constant τ . Under this classification, the first synaptic configuration, with high g_{syn}^{max} and low τ (0.1 mS and 2 ms, respectively), has been already tested (Fig. 7 A) and, as discussed, produced an unsatisfactory result. The second synaptic configuration, with high values of both g_{syn}^{max} and τ (0.1 mS and 8 ms), led to a stronger cortical excitation on the CT neuron, thus causing the inactivation of sodium currents and impeding the transmission of afferent signals (results not shown). The third synaptic configuration, when the values

were both low (0.01 mS and 2 ms), caused no meaningful change in the firing threshold (results not shown).

The desired behaviour was finally achieved by setting a high time constant value and a low maximum conductance. The results obtained after setting g_{syn}^{max} = 0.01 mS and τ = 8 ms between the excitatory cortical neuron and CT neuron are shown in Fig. 7 B. The behaviour here was the same as that shown in panel A until t = 400 ms, or in other words, until 3 receptors were activated. This generated a subthreshold input but elicited a response in the CT neuron due to the cortical excitatory effect. However, the membrane sensitization lasted less than 100 ms (until 500 ms), and thereafter, the CT neuron did not produce spikes. In the last interval, without afferent stimulation, no spikes were generated. We have finally discovered a synaptic configuration allowing facilitation without blockade. How to reconcile the fact that synaptic parameters required to obtain blockade during sleep differ from those required to obtain facilitation in wakefulness will be considered in the Discussion Section.

Although cortical excitation is able to sensitize the CT neuron thus reducing the firing threshold, this facilitatory mechanism could not be sufficient if strong inhibition, inducing a substantial increase in the firing threshold, is also present. Such a situation must be avoided to achieve efficient facilitation. This can be done in two different ways: inactivation of cortical neurons responsible for such inhibition, or inhibition of those interneurons inhibiting CT neurons. The latter mechanism is supported by the discovery of interneurons being inhibited after cortical stimulation (see Section 3.1). We set up a simulation to test this mechanism. The proposed circuitry and the simulation results are shown in Fig. 8. The input was made up of four receptors establishing synapses with g_{syn}^{max} = 0.01 mS. For the other connections we set g_{syn}^{max} = 0.3 mS between interneuron I1 and CT neuron, and g_{syn}^{max} = 0.01 mS between interneuron I2 and interneuron I1. Cortical inhibition was activated at 400 ms. We activated the disinhibiting mechanism at 700 ms and observed that, as expected, interneuron IT1 was silenced, allowing the transfer of information through the CT neuron.
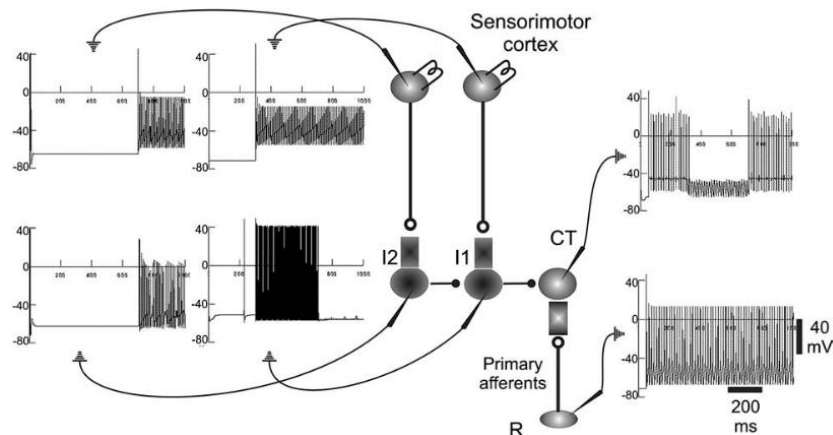

Fig. 8. Inhibition of interneurons leading to disinhibition of CT neurons. A CT neuron was inhibited from 300–700 ms after cortical stimulation and activation of interneuron I1. This interneuron, and therefore the inhibition on CT, was blocked by a second interneuron I2 from 700–1000 ms

How does disinhibition improve the facilitation of CT neurons? The circuitry that integrates the three descending pathways providing inhibition, excitation and disinhibition of CT neurons is shown in Fig. 9. We also connected, as proposed by Canedo et al. (2000), the cortical neuron in charge of cuneate excitation with the other one in charge of cuneate disinhibition. Synaptic contact between interneurons was set with g_{syn}^{max} = 0.1 mS and τ = 4 ms. Under activation of 3 receptors (0.005 nA) during 100–200 ms, there was no response in the CT neuron. After increasing the activation to 6 receptors in the interval 200–400 ms, the CT neuron generated action potentials thus activating, through the TC neuron, the excitatory cortical neuron. This neuron activated the disinhibitory cortical neuron, which, in turn, activated the corresponding cuneate interneuron. The final effect was partial inhibition of interneuron I1, which substantially decreased its activity. The most notable results corresponded to the interval between 400 and 600 ms, in which the activated receptors were reduced to 3. As before (see Fig. 7), the CT neuron remained depolarized, due to the cortical action, and transmitted information. However, depolarization

was then sustained during the entire interval (from 400 to 600 ms), in contrast to the findings shown in Fig. 7. This sustained effect is caused by the disinhibiting mechanism, which reduces the firing threshold and allows the cortical effect to elicit a sustained depolarization on the CT neuron. The simulation finalizes, after 600 ms, when stimulation is removed and the CT neuron ceases its activity.
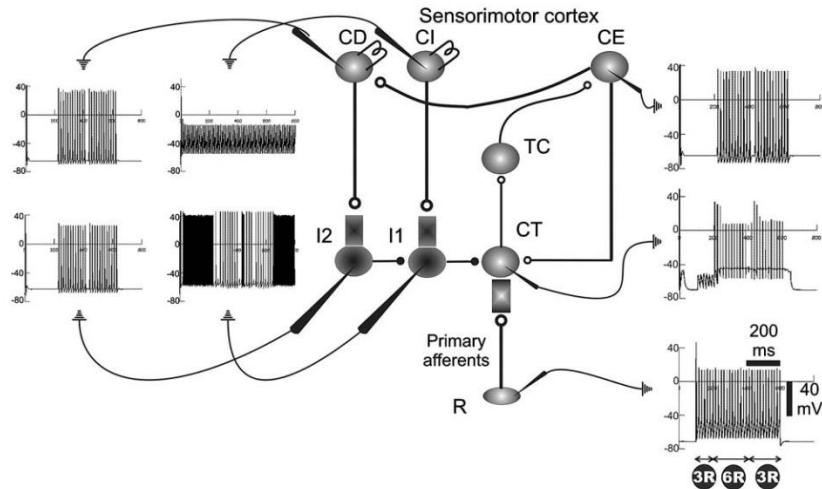

Fig. 9 Disinhibition as a mechanism for efficient facilitation. Cutaneous stimulation of 3 receptors (*R*) cannot overcome the filtering originated from the sensorimotor cortex. Six receptors (from 200–400 ms) were required to completely transmit the information. When the number of activated receptors was set back to 3, both cortical excitation and disinhibition facilitated the transmission of cutaneous information. Disinhibition guaranteed that the information was transmitted during the entire stimulation interval

4. Discussion

4.1. Corticocuneate connections and the DCN circuitry

The interneurons shown in Fig. 1 were introduced to ex- plain the cortical effects on cuneate neurons. The issue here is whether these neurons are also involved within the local CN circuitry or whether they do not participate in such local processing. Recent evidence supports the former hypothesis. Stimulation of the ML and SMC elicits short-latency excitation and longer-latency inhibition on CN interneurons (Canedo et al., 2000). Excitation is explained by means of recurrent connections originated from neighbouring lemniscal sites, whereas inhibition would involve a second interneuron since lemniscal and corticocuneate fibers are excitatory.

It is important to point out here that a similar microcircuit composed of TC neurons, reticular interneurons and local interneurons can also be found at the thalamic VPL (Steriade, 2001). The thalamic reticular nucleus may play a similar role to the shell in the medial zone of the CN, as both have interneurons that receive excitatory descending fibers originated in the SMC. Moreover, the cutaneous core of VPL could be compared to the core of the cuneate medial zone. In both regions, projection neurons, either cuneothalamic or thalamocortical, as well as local interneurons can be found. Thus it appears that a microcanonical structure is repeated throughout the somatosensory system, probably playing a similar processing role at different perceptual stages.

4.2. Functional interpretation

4.2.1. DCN and sleep states

Spindle patterns have been suggested to originate in the thalamus (McCormick and Bal, 1997 ; Steriade, 2001), then passed to the SMC and finally transmitted to the DCN (Mariño et al., 2000). It therefore seems plausible that the DCN could block the transmission of cutaneous information by means of a spindle-like rhythm (see Fig. 5). New experimental data are needed to demonstrate whether the DCN behaves in the same manner *in vivo* .

Furthermore, the DCN can follow the transition to deeper sleep states as the spindle rhythms are replaced by the delta rhythms (1–4 Hz) by means of the intrinsic properties of cuneate neurons. Mariño et

al. (2000) observed these rhythms in the DCN after deafferenting the pyramidal tract (which contains corticofugal fibers to DCN), indicating that cuneate neurons may intrinsically generate delta rhythms. Finally, cortical circuits would generate slow rhythms (< 1 Hz) and impose them onto subcortical structures (see Fig. 6). As shown in the simulations, the hyperpolarized cycle of this rhythm would be determined by excitatory descendant fibers impinging on interneurons exerting inhibitory influence on CT neurons, whereas the depolarized cycle would be determined by excitatory descendant fibers over CT neurons. These results imply that SSC and MC should show counter- phase synchronization.

4.2.2. DCN and wakefulness

In terms of information-processing, the CN can be under- stood as a spatio-temporal filter detecting changes from incoming inputs. Sánchez et al. (2001) have identified three main operations that the cuneate circuitry might perform: edge detection, signalling differences between intensity patterns applied to the skin; maximum edge detection, signalling differences between detected edges; and novelty de- tection, signalling changes between successive input pat- terns. This bottom-up processing can be further refined with top-down cortical processing acting over the existing DCN microcircuit through descendant fibers. We believe that when the DCN identifies regions where spatial or temporal changes occur, the SMC selects the output of these regions, thus allowing the transmission of information from selected cutaneous areas while suppressing information from others. This selection can be achieved through facilitation and improved through disinhibition. The suppression of activity can be achieved through filtering (inhibition of CT neurons). This attention mechanism, or gating, is also suggested for the VPL, thus favoring the idea that attention could operate at different stages in the nervous system (Britten, 1996) and specifically throughout the somatosensory sys- tem. A similar facilitation/filtering mechanism can be triggered by the local DCN circuitry. CT neurons responding to salient stimulated regions can reinforce their activity by ex- citing/facilitating neighboring neurons whereas suppressing the activity of distant stimulated sites. This bottom-up processing can be further reinforced through cortical descending fibers.

4.2.3. Transition from sleep to wakefulness

The transition from sleep to wakefulness may involve the modulation of potassium currents at the DCN from either the brain stem (Sotgiu and Margnelli, 1976) or cortical afferents (Martínez et al., 1995). Such a mechanism may depolarize CT neurons and therefore change the effects of inhibitory synapses. At low levels of hyperpolarization, inhibition does not activate I_h or deinactivate I_T currents, and therefore sustained hyperpolarization rather than post-inhibitory bursting rebound is observed. Different inhibitory levels would deter- mine different sustained hyperpolarized levels, which allow a variable firing threshold required for filtering operations.

Moreover, we have shown that the facilitation mechanism requires excitatory connections with a specific combination of both maximum conductance and time constant, other than those operating during sleep conditions. How can this be achieved? We propose two different scenarios: either the synaptic parameters also change during the transition from sleep to wakefulness, or there exist two types of excitatory synapses, one related to the blocking proper- ties required during sleep and the other related to the sustained depolarization required during wakefulness. While there is, as far as we know, no experimental evidence to support the former hypothesis, there may be a physiological basis for the latter: Martínez et al. (1995) reported that two types of descendant fibers make synaptic contacts within the core zone of the medial cuneate. The first type runs over the corticospinal tract, made up by fast conducting fibers, and could be in charge of facilitation during wakefulness; the second type are slow conducting corticocuneate fibers, in charge of blocking afferent information during sleep. Additional experiments are required to confirm this hypothesis.

4.2.4. Beyond mountcastle's view: sensorimotor control and active perception

The specific role of somatosensory and motor cortices in DCN is an important issue. Apart from their participation in attention, it appears that motor signals may differ from somatosensory signals in terms of their goal. It has been hypothesized (Canedo et al., 2000) that motor feedback may encode: (1) signals targeted to required motoneurons to per- form touch/grasp actions, (2) predictions about which peripheral receptors will be stimulated in order to prepare CT neurons to process cutaneous information during active perception tasks. This predictive task could be accomplished through facilitation mechanism that would depolarize CT neurons to process afferent signals. Motor signals would be sent through corticospinal fibers, which show high conduction speeds and therefore allow fast coordination between movement and cutaneous perception.

On the other hand, SMC signals, responsible for tonic inhibition of CT neurons, can also be interpreted beyond the simple filtering approach. Recent models (Rao and Ballard, 1999) for the visual system have explained descendant inhibition as carrying predictive information about cur- rent inputs. The mechanism would work as a Kalman filter, in which the error signal generated between the expected in- put and the real input is used to improve future predictions. We may therefore consider the level of inhibition of CT neurons as encoding the prediction generated by the SMC. If this is true we would have to analyze how the predictions are encoded and how the error signals might be generated to improve the predictive power of the system.

4.3. Contributions

In short, the main contributions of this paper are:

1. A computational model of the corticocuneate circuitry.
2. Explanation of the blockade of afferent sensory information by the model.
3. Evidence that the same circuitry can operate during wakefulness (filtering and facilitation) when the synaptic parameters are appropriately tuned.
4. Evidence that the SMC filters the ascending sensory in- formation through the cuneate nucleus by tonically inhibiting the CT neurons and thus modifying their firing threshold.
5. Evidence that facilitation requires corticocuneate excitatory connections with high time constants, as well as low maximum conductances to achieve sustained depolarization.
6. Evidence that efficient facilitation requires inhibition of inhibitory neurons, i.e a disinhibitory mechanism for CT neurons.

5. Future work

A computational model integrating DCN local circuitry and corticocuneate connections needs to be developed. The DCN circuitry is able to perform spatial as well as temporal filtering on cutaneous input (Sánchez et al., 2001). The following questions remain: How can this processing be modified when introducing the cortical modulation? Can the sensorimotor cortex shift attention to salient dynamic patterns? Moreover, recent discoveries about the existence of glycinergic and gabaergic interneurons should also be considered (Aguilar et al., 2003). We need to study the impact of these types of neurons in our model. Are they associated with different inhibitory effects? Additional experiments and simulations considering the whole corticocuneate circuitry are required for answering these questions.

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