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Eduardo Sánchez, Senén Barro, Jorge Mariño, Antonio Canedo ...+1 more authors

Institutions: University of Santiago de Compostela

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Modelling the circuitry of the Cuneate Nucleus

Eduardo Sánchez[1], Senén Barro[1], Jorge Mariño[2], Antonio Canedo[2], and Pablo Vázquez[1]

[1] Grupo de Sistemas Intelixentes (GSI)
Departamento de Electrónica e Computación, Facultade de Físicas,
Universidade de Santiago de Compostela,
15706 Santiago de Compostela, Spain
{elteddy, elsenen, elpablo}@usc.es
http://elgsi.usc.es/index.html
[2] Departamento de Fisioloxía, Facultade de Medicina,
Universidade de Santiago de Compostela,
15706 Santiago de Compostela, Spain
{fsancala, xmarinho}@usc.es

Abstract. Experimental data recorded in cat *in vivo* offer a new picture of the cuneate nucleus. Classically defined as a simple relay station, the cuneate nucleus is currently seen as a fundamental stage in somatosensory information processing. Intracellular and extracellular recordings have revealed a complex circuitry established by cuneothalamic cells, interneurons and afferent fibers from the sensorimotor cortex. As a result of electrophysiological work, some circuits have been hypothesized in order to explain the data. In this paper we present a computational model designed and developed in order to test the validity of the proposed circuit in [15]. The results of the computer simulations support the predictions.

1 Introduction

The dorsal column nuclei (DCN): cuneate and gracilis, are the first relay station of the dorsal column-medial lemniscal system. The cuneate nucleus receives information from the forelimbs and the anterior part of the body. The projection neurons in the middle part of the cuneate project to the contralateral ventroposterolateral (VPL) thalamic nucleus through the medial lemniscus. The middle cuneate is constituted by two morphologically distinct regions: a core or cluster zone and a shell. The cluster zone receives mostly cutaneous input and it is basically formed by projection or cuneothalamic cells [13]. The shell receives a combination of cutaneous and deep (mostly muscular) input and it is mostly formed by local neurons (interneurons) [6].

The two major inputs to the CN are made up of primary afferents and corticocuneate fibers from the contralateral sensorimotor cortex running in the pyramidal tract [2, 22]. The primary afferents carrying information from sensory receptors establish glutamatergic excitatory synapses with cuneothalamic neurons

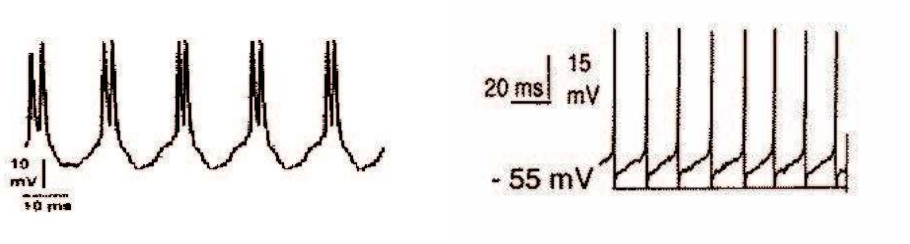

Fig. 1. Intracellular recordings *in vivo* of the spontaneous activity of cuneate neurons: cuneothalamic cells (left) and interneurons (right)

[19]. The corticocuneate fibers establish excitatory synapses with interneurons and projection cells.

1.1 Experimental data

Andersen et al. [1] found that sensorimotor cortical stimulation inhibited cuneothalamic cells and proposed a model of the integration of the corticocuneate input within the cuneate nucleus. By this model, corticofugal fibers would contact cuneothalamic cells through an inhibitory interneuron. In addition, they postulated a different pool of inhibitory cuneate interneurons exerting presynaptic inhibition on the terminals of the primary afferent fibers. Therefore, the sensorimotor cortex would affect the ascending sensory transmission through the cuneate by inhibiting the cuneothalamic cells both pre- and postsynaptically.

Intracellular and whole-cell techniques were recently used *in vivo* to study the properties of cuneate cells [4, 14]. It was found that the cuneate neurons posses two modes of activity (see figure 1): bursting and tonic [4]. During deep sleep and anaesthesia, the cuneate neurons show oscillatory bursting activity. This behavior changes to the tonic mode when injecting depolarizing current or stimulating their peripheral receptive fields. Different ionic channels, including a low-threshold calcium and a hyperpolarization-activated cation channel, have been postulated to explain this behaviour [4].

Simultaneous recordings were accomplished to study the influence of the sensorimotor cortex over the cuneate cells (see [3] for a review). In these preparations, an electrical stimulus was applied to specific sensorimotor cortical regions while the intracellular neuronal activity was recorded in the CN. Under this protocol three different responses at the CN were seen [15]: excitation (figure 2) and inhibition (figure 3) of cuneothalamic cells, hyperpolarization and burst generation of cuneothalamic cells (figure 3), and inhibition of presumed interneurons (figure 3). These results, which extend those from Andersen and colleagues, make it possible to hypothesize about the existence of a specific circuitry in which three different descending routes can induce distinct actions on the cuneate nucleus. A **potentiation signal** triggered by direct excitation of cuneothalamic cells, thus

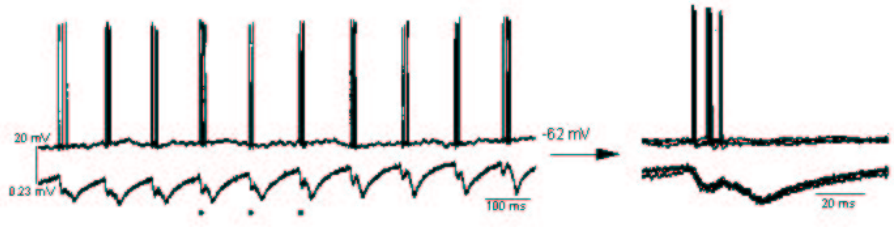

Fig. 2. Sensorimotor cortex induces direct excitation on cuneothalamic cells: cortical activity (lower part) and cuneothalamic response (upper part).

enhancing their capability to transfer sensory information to the thalamus. This phenomenon can be associated with a **disinhibiting signal** to shape the receptive fields by activating an interneuron which, in turn, inhibits other inhibitory interneuron. Finally, an **inhibiting signal** is responsible to filter unwanted information.

1.2 Current questions

The diagram shown in figure 3 represents a plausible circuit intending to explain the experimental results. The lack of both anatomical and pharmacological data from the CN is an obstacle to test the validity of such circuit. Due to this, some questions arise naturally: can the hypothetized ionic currents generate the oscillatory and tonic behaviors described for the cuneate neurons?, is the model shown in figure 3 adequate to explain the recordings obtained from the cat?.

In this work we propose a computational model with the objective of adding new evidence about the validity of the scheme shown above. We have developed detailed descriptions of the neurons that play a role in the Cuneate and tested the results of that cells under similar conditions to those described in cats. After that, we have made up a circuit following the scheme presented in figure 3. In what follows we present the mathematical model, the results of the simulations and a discussion of the results pointing out the implications of the model.

2 The model

Four levels of description are needed to deal with the questions proposed here: the circuit level, the synaptic level, the neuron level, and the membrane level.

- Circuit level. In figure 4 the circuit model is described. It is composed of sensory receptors, primary afferents, cuneothalamic neurons, interneurons, cortical cells and descending fibers from the Cortex. We have used a total of 7 neurons in our model.

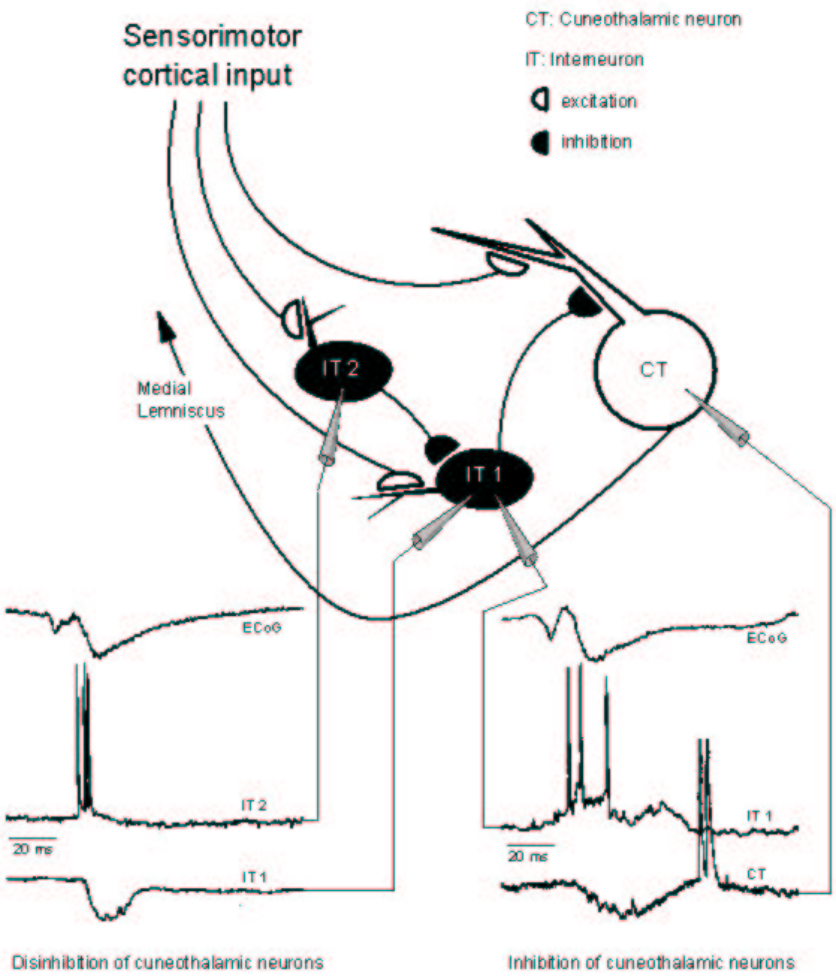

Fig. 3. Simultaneous recordings at sensorimotor cortex and at cuneate nucleus after electrical stimulation in the Somatosensory Cortex: disinhibition (left) and inhibition (right) over projection neurons. ECoG means electrocorticogram

– Synaptic level. In order to model the chemical synapse we have used a mathematical function called the *Alpha function*. This is used to represent the conductance associated to the synaptic current. This conductance is given the task of generating the postsynaptic potential, which is originated after the activation of dendritic receptors [11]. The mathematical expression is:

$$g_{syn}(t) = \alpha \frac{t - onset}{\tau} e^{-\frac{t-onset-\tau}{\tau}} \quad (1)$$

where α is a constant, *onset* the start time and τ the constant time. The value of the synaptic conductance will be zero if the presynaptic potential is below a certain threshold and will be equal the *Alpha function* above such threshold. What is more, g_{syn} determines the dynamics of the synaptic current I_{syn} defined by:

$$I_{syn}(t) = g_{syn}(t)(V - V_{syn}) \tag{2}$$

where V_{syn} represents the rest potential for the synaptic receptors.
In our model we have excitatory and inhibitory connections. These synapses can be modeled by setting V_{syn} as possitive and negative values respectively.

– Neuron Level. We have used a multicomparmental approach to model the neurons [18]. The membrane potential for each compartment is computed by using the following expression:

$$C\frac{\partial V}{\partial t} = -I_m - I_{syn} - I_{inject} - \frac{(V^{'} - V)}{R_a^{'}} - \frac{(V^{''} - V)}{R_a^{''}} \tag{3}$$

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 $\frac{(V^{'}-V)}{R_a^{'}}$ and $\frac{(V^{''}-V)}{R_a^{''}}$ represents the axial current between each compartment and its adjacent ones.
The compartments and currents used to model the neurons of the figure 4 are the following:

- Sensory receptors and cortical cells. These neurons are modeled with two compartments representing the soma and the axon. The membrane current for both compartments is the sum of the contributions of a sodium current and a potassium current. Therefore we have $I_m = I_{Na} + I_K$.
- Cuneothalamic cells. Modeled with three compartments representing the soma and two dendritic branches. For the soma we have a sodium current I_{Na} [9], a potassium current I_K [16], a high-threshold calcium current I_L [12], a calcium-activated potassium current I_{ahp} [23], a hyperpolarization-activated cation current I_h [17] and finally a low-threshold calcium current I_T [5]. The membrane current will be $I_m = I_{Na} + I_K + I_L + I_{ahp} + I_h + I_T + I_l$[1]. The dendritic branches are set with passive currents only.
- Interneurons. These are modeled with three compartments representing the soma, a dendritic branch and the axon. For the soma we have similar currents to those in cuneothalamic cells with the addition of the slow potassium current I_A [10] and the substitution of I_{ahp} for other calcium-activated current I_C [23]. The membrane current is $I_m = I_{Na} + I_K + I_L + I_T + I_C + I_h + I_A + I_l$. The axon and the dendritic branch content only passive currents.

– Membrane Level. We have used the Hodgkin-Huxley (HH) formulation as the mathematical model for describing the ionic currents. The HH general expression for an ionic current related to a membrane channel is:

[1] I_l represents the contribution of currents associated to passsive channels

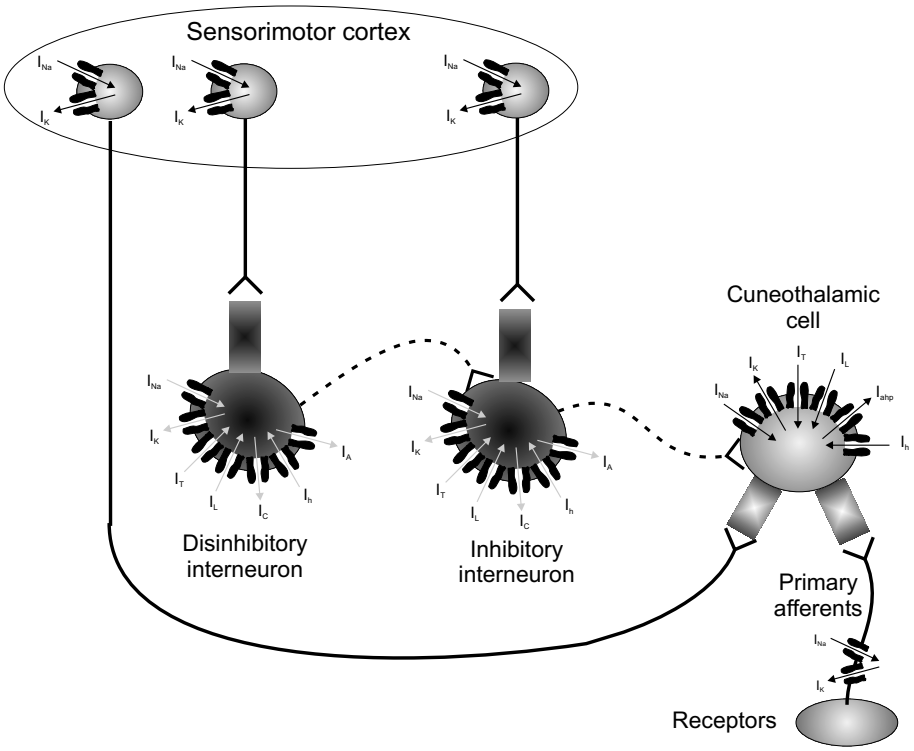

Fig. 4. The circuit model: sensory receptors, primary afferents, cuneothalamic cells, interneurons and cortical cells. The main features are shown: ionic currents, compartments for each cell and synaptic connections

$$I_{ion} = g_{ion}^{max} m^p h^q (V - V_{ion}) \tag{4}$$

where g_{ion}^{max} represents maximum conductance, V_{ion} the resting potential for such ion, m the probability of an activation gate being open, h the probability for an inactivation gate being open, and p and q the number of activation and inactivation gates of this ionic channel.
In the appendix we present the mathematical expressions we have used to describe the ionic currents in our simulations.

2.1 Simulation parameters

Parameters for the simulations are shown in tables 1 and 2. Maximun conductances and resting potentials are presented for each ionic current. Some conductance values have been adapted according to the features of the Cuneate cells.

	I_{Na}	I_K	I_L	I_T	I_{ahp}	I_h	I_l
$g_{ion}^{max}(nS)$	10	2.5	0.01	0.1	1.2	0.05	0.001
$V_{ion}(mV)$	40	-70	100	100	-70	-43	-62

Table 1. Ionic current parameters for the cuneothalamic neurons: maximun conductances and resting potentials.

	I_{Na}	I_K	I_L	I_T	I_C	I_h	I_A	I_l
$g_{ion}^{max}(nS)$	5	1	0.125	0.125	1	1.5	1.5	0.001
$V_{ion}(mV)$	60	-80	50	50	-80	-43	-80	-62

Table 2. Ionic current parameters for the interneurons: maximun conductances and resting potentials.

2.2 Computational Tools

For the simulations we have used the *Neuron* simulator program [7]. This program, developed by M. Hines and J. W. Moore, offers tools for implementing realistic neuronal models from molecular level to system level. The neurons are thought as sets of sections conceptually similar to the compartments of W. Rall. In order to implement the model, the user must design and write a script based on a language called MODL (MOdel Description Level). After writing and compiling the program, the simulator allows the user to plot voltage and current graphs, determine the total time of the simulation, change current and synaptic parameters or carry out voltage and current clamp experiments. The simulations use the Hines integration method, a fast procedure that optimizes the process by combining the benefits of both Crank-Nicholson and Euler methods.

The simulations were carried out on a PC with a 333 MHz Pentium II processor.

3 Results

3.1 Spontaneous activity

As can be seen in figure 1, cuneothalamic activity under anaesthesia is characterized by an oscillation composed of a deep hyperpolarization followed by a burst of spikes. In the model we have obtained similar behaviour by combining a set of ionic currents inspired by those found in thalamocortical neurons (see figure 5). An inward cation current and a low-threshold calcium current are responsible for recovering from hyperpolarization. Spikes are generated by a sodium current and repolarization is attributed to a typical potassium current. Hyperpolarization is driven by a high-threshold calcium current and a calcium-dependent potassium current.

The interneuron shows an oscillation with a single spike followed by a short hyperpolarization and a long resting period. Sodium and potassium currents

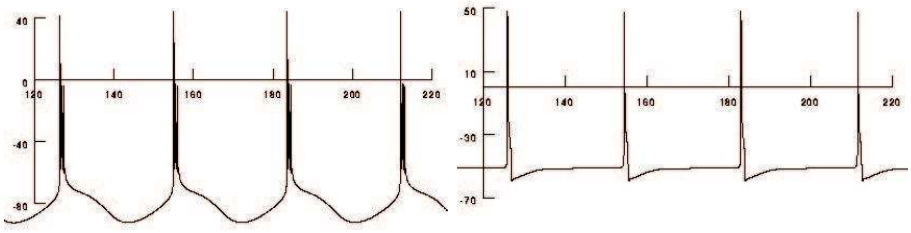

Fig. 5. Computer simulations of the spontaneous activity of cuneate neurons for 100 miliseconds: cuneothalamic cells (left) and interneurons (right). Voltage is plotted in milivolts

have been used to model the spike and a voltage dependent potassium current has been introduced to obtain the hyperpolarization. The fast recovery and the long interspike period have been explained by the existence of an inward cation current and a slow potassium current. It has been suggested that the later plays a fundamental role in determining oscillation frequency.

A detailed explanation of the currents and how they play a role in the potential membrane generation can be found in [20, 21].

3.2 Inhibition of cuneothalamic cells

Cortical neurons were depolarized by using electrical stimulation (1 nA). As a result the inhibitory neuron of the DCN, forced into a silent state by increasing the membrane resting potential and the passive currents, responds by generating a couple of spikes (see figure 6). The role of this neuron it to inhibit the activity in the cuneothalamic neuron by evoking an hyperpolarization at the soma. As a consecuence, I_h and I_t are activated and a burst of spikes is seen.

This mechanism can lead to a depression of sensory information when the cuneothalamic cell is operating in the tonic mode. In this case the simulations show how the projection cell is forced by the cortex to change from tonic to oscillatory activity (data not shown).

3.3 Disinhibition of cuneothalamic cells

As it is shown in figure 3, cortical efferents can inhibit the inhibitory interneurons. In order to explain this findings a second interneuron has been proposed to operate over the original one. In figure 6 we show how the model reproduces the results obtained experimentally. Both interneurons were forced to be silent and we have injected current (1 nA) in a cortical neuron in order to see the results. The hyperpolarization of the inhibitory interneuron could be a mechanism to ensure the quality of the sensory information carried by the projection cell.

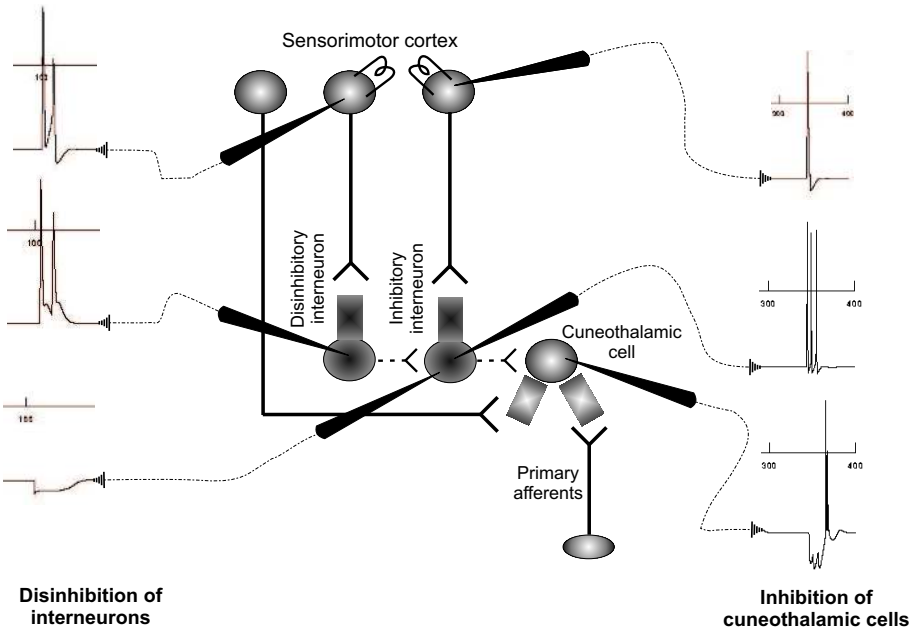

Fig. 6. Simulations to study the influence of the sensorimotor cortex over the cuneate nucleus: disinhibition of interneurons (left side) and inhibition of cuneothalamic cells (right side). Cortical behaviour is reproduced as it would be seen in an intracellular recording. The reader must notice the difference when comparing with the extracellular response shown in figure 3

3.4 Potentiation of ascendant information

The somatosensory cortex can induce direct excitation over the cuneothalamic neurons. In figure 7 we show the results of the simulation carried out in order to test this possibility. Again we have manipulated the membrane potential of the projection cell to avoid spontaneous oscillations. When we electrically stimulate in the cortex, a group of spikes appeared in the soma of the projection cell. This mechanism can be used by the sensorimotor cortex to increase the firing rate of the cells related to areas associated with useful information.

4 Discussion

The proposal shown in figure 3 gains credit after the simulations presented in this work. Not only the models of individual neurons show a behavior similar to those observed *in vivo*, but also the interconnections and the predictions about the existence of disinhibitory interneurons led to satisfactory results. If this scheme is finally confirmed to be true it would have profound physiological consequences. It would demonstrate new mechanisms in which the cortex can influence and

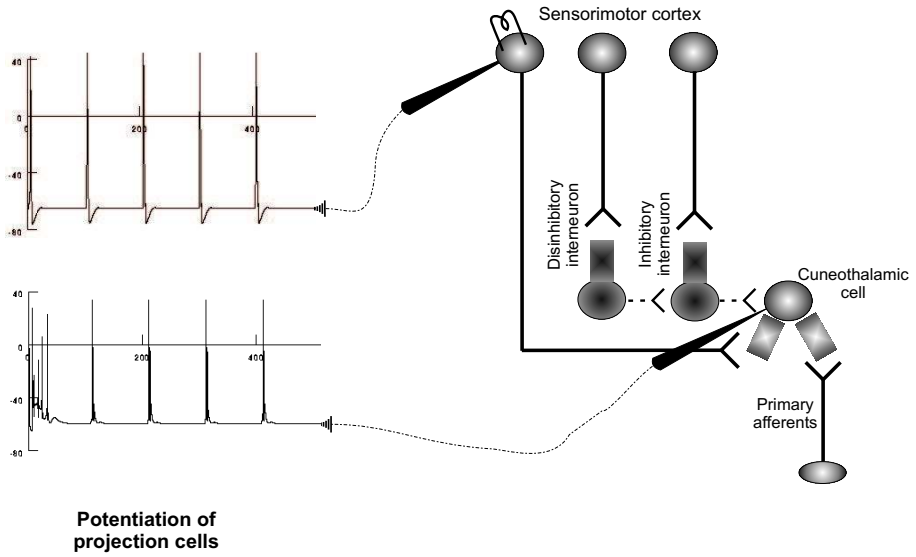

Fig. 7. Potentiation of ascendant information due to the influence of the sensorimotor cortex

modulate the flow of information through the prethalamic nuclei. In such a way we could infer that there exist high level commands to apply when there exist useful or useless information. In case of the first situation the cortex could potentiate the transmission of information through two mechanisms: a direct excitation of cuneothalamic neurons and a disinhibition through interneurons. On the other hand, if the cortex is not interested in a particular sensory input it can inhibit cuneothalamic neurons through inhibitory interneurons.

There exist more experimental data to be used to test our model. Simultaneous recordings in cortex and in Cuneate Nucleus reveals a similar pattern of oscillations: from slow rythms (<1Hz) to spindle rythms (in the range of 7-14 Hz)[14]. Some questions to be answered in future experimemts will be if our model can explain how the CN neurons can generate intrinsic oscillations and how the slow rythms can be induced by the cerebral cortex.

Other aspect to be studied by computer simulations will be the capability to predict new features. For instance, what is the relation between information frequency and tonic inhibition induced by the cerebral cortex in anaesthetized conditions. How much intensity must have the stimuli to overcome the threshold imposed by the cortex in sleeping conditions? What about the frequency coding?

The answers to these questions will aid to clarify our knowledge about the role of the cuneate nucleus in the processing of somatosensory information. We are sure that computational simulations will be a valuable tool to get those answers.

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Appendix: Mathematical expressions for ionic currents

Mathematical expression for cuneothalamic cells:

– Sodium current I_{Na}

$$I_{Na} = g_{Na}^{max} m_{Na}^3 h_{Na}(V - V_{Na}) \tag{5}$$

$$\begin{aligned} \alpha_m = \frac{1.28(V+38)}{1-e^{(\frac{-(V+38)}{5})}} \quad \beta_m = \frac{-1.24(V+38)}{1-e^{(\frac{-(V+38)}{5})}} \\ \alpha_h = 0.32e^{(\frac{-(V+55)}{15})} \quad \beta_h = \frac{41.4}{1+e^{(\frac{-(V-17)}{21})}} \end{aligned} \tag{6}$$

– Potassium current I_K

$$I_K = g_K^{max} m_K^4 (V - V_K) \tag{7}$$

$$\alpha_m = \frac{0.1(-45-V)}{e^{\frac{(-45-V)}{5}} - 1} \; \beta_m = 1.7e^{\frac{(-50-V)}{40}} \tag{8}$$

– High-threshold calcium current I_L

$$I_L = g_L^{max} m_L (V - V_{Ca}) \tag{9}$$

$$\alpha_m = \frac{16}{1+e^{-(V+30)}} \; \beta_m = \frac{0.004(V-1.31)}{e^{\frac{V-1.31}{5.36}} - 1} \tag{10}$$

– Low-threshold calcium current I_T

$$I_T = g_T^{max} m_T^2 h_T (V - V_{Ca}) \tag{11}$$

$$\begin{array}{cc} m_\infty = \frac{1}{1+e^{\frac{-(V+52)}{6.2}}} & \tau_m = 0.0025(\frac{1}{e^{\frac{-(V+132)}{16.7}}+e^{\frac{V+16.8}{18.2}}} + 0.612) \\ h_\infty = \frac{1}{1+e^{\frac{V+75}{4}}} & \tau_h = 1 \end{array} \tag{12}$$

– Calcium-dependent potassium current I_{ahp}

$$I_{ahp} = g_{ahp}^{max} m_{ahp}^2 (V - V_K) \tag{13}$$

$$\alpha_m = 10^8 [Ca]^2 \ \beta_m = 10 \tag{14}$$

– Hyperpolarization-activated cation current I_h

$$I_h = g_h^{max} m_h (V - V_h) \tag{15}$$

$$m_\infty = \frac{1}{1+\frac{75+V}{5}} \ \tau_m = \frac{0.1}{e^{-14.59-(0.086V)}+e^{-1.87+(0.007V)}} \tag{16}$$

Mathematical expressions for interneurons. Only I_C and I_A are described:

– Calcium-dependent potassium current I_C

$$I_C = g_C^{max} m_C (V - V_K) \tag{17}$$

$$\alpha_m = 640 [Ca]_{in} e^{\frac{V}{24}} \ \beta_m = 0.06 e^{-\frac{V}{24}} \tag{18}$$

– Slow potassium current I_A.

$$I_A = g_A^{max} m_A^4 h_A (V - V_K) \tag{19}$$

$$\begin{array}{cc} m_\infty = \frac{1}{1+e^{\frac{-60-V}{8.5}}} & \tau_m = \frac{0.1}{e^{\frac{V+35.8}{19.7}}+e^{\frac{-(V+79.7)}{12.7}}} + 0.037 \\ h_\infty = \frac{1}{1+e^{\frac{V+78}{6}}} & \tau_h = 1 \end{array} \tag{20}$$