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Localization of CCK Receptors in Thalamic Reticular Neurons: A Modeling Study

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Sohal, Vikaas S., Charles L. Cox, and John R. Huguenard. Localization of CCK receptors in thalamic reticular neurons: a modeling study. *J. Neurophysiol.* 79: 2827–2831, 1998. In an earlier experimental study, intracellular recording suggested that cholecystokinin (CCK) suppresses a K^+ conductance in thalamic reticular (RE) neurons, yet the reversal potential of the CCK response, revealed using voltage clamp, was hyperpolarized significantly relative to the K^+ equilibrium potential. Here, biophysical models of RE neurons were developed and used to test whether suppression of the K^+ conductance, g_K, can account for the CCK response observed in vitro and also to determine the likely site of CCK receptors on RE neurons. Suppression of g_K in model RE neurons can reproduce the relatively hyperpolarized reversal potential of CCK responses found using voltage clamp if the voltage clamp becomes less effective at hyperpolarized potentials. Three factors would reduce voltage-clamp effectiveness in this model: the nonnegligible series resistance of the voltage-clamp electrode, a hyperpolarization-activated mixed cation current (I_h) in RE neurons, and the dendritic location of CCK-sensitive K^+ channels. Although suppression of g_K in the dendritic compartments of model RE neurons simulates both the magnitude and reversal potential of the CCK response, suppression of g_K in just the somatic compartment of model RE neurons fails to do so. Thus the model predicts that CCK should effectively suppress K^+ conductance RE neuron dendrites and thereby regulate burst firing in RE neurons. This may explain the potent effects of CCK on intrathalamic oscillations in vitro.

INTRODUCTION

Thalamocortical rhythm generation depends on reciprocal interplay between thalamic and cortical circuits (reviewed by Steriade et al. 1993), and the thalamic reticular nucleus appears to play a key role especially in sleep spindles (Steriade et al. 1987) and in animal models of absence epilepsy (Avanzini et al. 1992; Inoue et al. 1993). A number of neuroactive agents can modulate reticular (RE) neuron activity and thus strongly influence thalamic (and presumably thalamocortical) rhythm generation (Cox et al. 1997; Lee and McCormick 1996, 1997). Cholecystokinin (CCK) is a neuropeptide found in thalamic and cortical neurons (Ingram et al. 1989) that project to RE (Jones 1985). In addition, CCK receptors are present in RE (Peleprat et al. 1987), and CCK profoundly modulates the duration of intrathalamic oscillations in vitro (Cox et al. 1997). This suggests that an understanding of CCK's actions on thalamic neurons may elucidate regulatory mechanisms for intrathalamic oscillatory activity. Intracellular recordings from thalamic RE neurons suggest that the CCK agonist, CCK8S, suppresses a K^+ conductance in these cells because the reversal potential of the CCK8S response changes when the external $[K^+]$ changes, and the CCK8S response is blocked by the potassium channel blocker Cs^+ (Cox et al. 1995). However, voltage-clamp recordings in this study revealed a reversal potential for the CCK8S response that was significantly more hyperpolarized than the equilibrium potential of potassium. Here we develop computational models based on intracellular data from RE neurons that demonstrate that suppression of K^+ conductance, g_K, in model RE neurons can produce the experimentally observed CCK response but only under specific conditions. One of these is that CCK must suppress g_K in the dendrites of RE neurons. Suppression of dendritic g_K may regulate the firing mode of RE neurons and the duration of intrathalamic oscillations.

METHODS

All of the simulations reported here were performed using NEURON (for more details, see Hines and Carnevale 1997). We simulated the behavior of RE neurons using 80- and 3-compartment models developed in an earlier study (Destexhe et al. 1996). The 80-compartment model was based on the biocytin-stained RE neuron shown in Fig. 1 of Huguenard and Prince (1992). The 3-compartment model had been generated from the 80-compartment model by collapsing several dendritic compartments into equivalent cylinders (Bush and Sejnowski 1993); because the membrane area of each equivalent cylinder did not equal that of the collapsed compartments, the passive membrane conductance and membrane capacitance in each equivalent cylinder were rescaled by a correction factor, $C_d = 3.78$ (Destexhe et al. 1996).

Model geometry and passive properties

The three compartments in the reduced model correspond to the soma, proximal dendrites, and distal dendrites, as diagrammed in Fig. 1. Each compartment had a membrane capacitance, $C_m = 1\ \mu F/cm^2$, axial resistance of 260 Ω/cm, and a leak current with conductance, g_{leak}, and equilibrium potential, E_{leak}. The leak was assumed to result from a parallel conductance with Na^+ and K^+ components ($E_{Na} = +58$ mV and $E_K = -105$ mV). We used E_{Na}, E_K, E_{leak}, and g_{leak} to calculate the passive Na^+ and K^+ conductances, g_{Na} and g_K. The effects of CCK on a compartment were modeled by reducing g_K in that compartment, and calculating the resulting g_{leak} and E_{leak}.

Inward rectification is observed commonly in RE neurons both in vivo (Mulle et al. 1986) and in vitro (Contreras et al. 1993; McCormick and Prince 1986). To model rectification, we introduced a hyperpolarization-activated, mixed cationic current, I_h, in the soma. For the purposes of these simulations we assumed that I_h in RE cells responded to changes in voltage instantaneously, unlike the slow activation of I_h in relay neurons (Pape and McCormick 1989). This simplified I_h model provided an excellent fit to both current clamp and voltage clamp data (see Figs. 2 and 3).

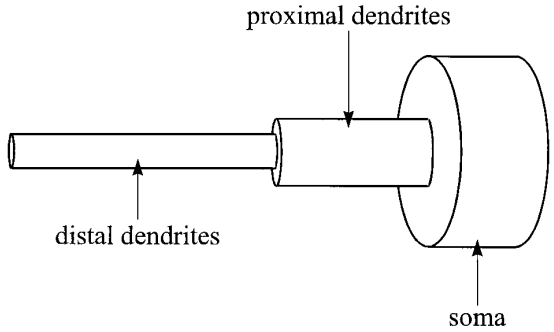

FIG. 1. Geometry of a 3-compartment model reticular (RE) neuron. Three compartments, which represent the soma, proximal dendrites, and distal dendrites, had the following dimensions: length = 34 μm and diameter = 14 μm (soma); length = 103 μm and diameter = 5.6 μm (proximal dendrites); length = 191 μm and diameter = 3.1 μm (distal dendrites). This 3-compartment model had been generated from an 80-compartment model by collapsing several dendritic compartments into equivalent cylinders.

The voltage dependence of I_h was described using the standard Boltzmann equation

$$I_h = \frac{g_h(E_h - V)}{[1 + e^{(V-V_{1/2})/k)}]^N} \quad (1)$$

Based on earlier mathematical analysis of I_h in thalamic relay neurons, we assumed $N = 1$ (Huguenard and McCormick 1992). This current would functionally be very similar to an inwardly rectifying potassium current (cf Williams et al. 1988).

We simulated voltage-clamp recordings from model RE neurons. I_{vc}, the clamping current injected by the simulated voltage clamp into the midpoint of the model neuron's soma was given by

$$I_{vc} = (V_c - V_m)/R_s \quad (2)$$

where V_c is the clamp's command voltage, V_m is the membrane potential of the soma, and R_s is the series resistance of the voltage clamp electrode. This simplification relies on the assumption that during single-electrode voltage clamp, the headstage voltage has settled before voltage measurement (see Cox et al. 1995 and DISCUSSION). Unless otherwise stated, R_s = 10 MΩ. We obtained *I-V* curves by recording the clamping current while gradually changing the command voltage. The duration of simulated voltage ramps (2 s) was chosen so that the value of dV/dt (and hence the amount of capacitive current) would be approximately the same in simulations and experiments.

RESULTS

Initially we compared results from the 80- and 3-compartment models and found no significant differences. Therefore all of the following results are from the three-compartment model.

Inward rectification in RE neurons

RE cells in rat typically exhibit rapidly activated inward rectification as has been observed in cat (Contreras et al. 1993; Mulle et al. 1986) and in guinea pig (McCormick and Prince 1986). As this rectification occurs in a voltage range that overlaps with that expected for the potassium equilibrium potential, it was necessary to characterize the voltage dependence of rectification for the purposes of the simulations. In Fig. 2*A* are shown intracellular recordings from an RE neuron during current injection, and Fig. 3, *A* and *B* (*top*: noisy traces), shows ramp *I-V* curves from two voltage-clamped RE neurons. Inward rectification is evidenced by the following: *1*) in Fig. 2*A*, although the amount of current injected on successive traces differs by a fixed increment, the distance between successive traces becomes smaller at more hyperpolarized potentials, i.e., the incremental hyperpolarization resulting from a fixed increment of current is decreased; *2*) also in Fig. 2*A*, the membrane time constant becomes shorter at more hyperpolarized potentials; and *3*) the experimental *I-V* curves shown in Fig. 3, *A* and *B*, become more steep at increasingly hyperpolarized potentials. These observations all suggest that RE neurons contain a hyperpolarization-activated current. Furthermore, the effects of this current become evident within 20 ms in Fig. 2*A*. This suggests that inclusion of an instantaneous hyperpolarization-activated current in our model RE neurons is physiologically reasonable.

Comparison of physiological data to models with CCK effects localized in different compartments.

We fitted ramp *I-V* curves from two RE neurons (Cox et al. 1995). For each neuron, two *I-V* curves (1 each in the presence and absence of CCK) had been obtained. The control responses for each neuron were fitted by adjusting six model parameters (g_{leak}, V_{rest}, g_h, E_h, $V_{1/2}$, and k) using the downhill simplex method. The parameters obtained are shown in Table 1 and remained fixed through all subsequent simulations.

Figure 2*B* compares simulated responses of RE *neuron 1* during current injection to the responses of the actual RE neuron shown in Fig. 2*A*. The burst of action potentials elicited by depolarizing current injection and burst afterhyperpolarization in *A* is characteristic of RE neurons (Avanzini et al. 1989). Again, in both Fig. 2, *A* and *B*, incremental hyperpolarizations resulting from fixed increments of current are reduced at more hyperpolarized potentials. In both Fig. 2, *A* and *B*, the effects of I_h seem to begin at membrane potentials around −75 mV and are associated with a shortening of the membrane time constant. Figure 3 *(top)* shows the experimental and simulated *I-V* curves for two RE neurons in the absence of CCK agonist (control). Both simulated *I-V* curves have the characteristic appearance of the intracellularly recorded curves, becoming more steep at hyperpolarized potentials. Thus the simulated effects of our simplified I_h are consistent with intracellular data. This confirms the adequacy of our six-parameter model for RE neurons.

Using the parameters obtained by the simplex fitting of the control *I-V* curve, we simulated CCK application to both model RE neurons in four different ways: first, we reduced g_K in all compartments equally; second, we selectively reduced somatic g_K, but not dendritic g_K; third, we reduced g_K by an equal amount in both dendritic compartments but left somatic g_K unchanged; and fourth, we decreased g_K in only one of the two dendritic compartments. We found that decreasing g_K in the proximal dendritic compartment produced the same results as decreasing g_K in the distal dendritic compartment and hence will not elaborate on the results of decreasing g_K unequally in the two dendritic compartments.

Each of the remaining three conditions is characterized

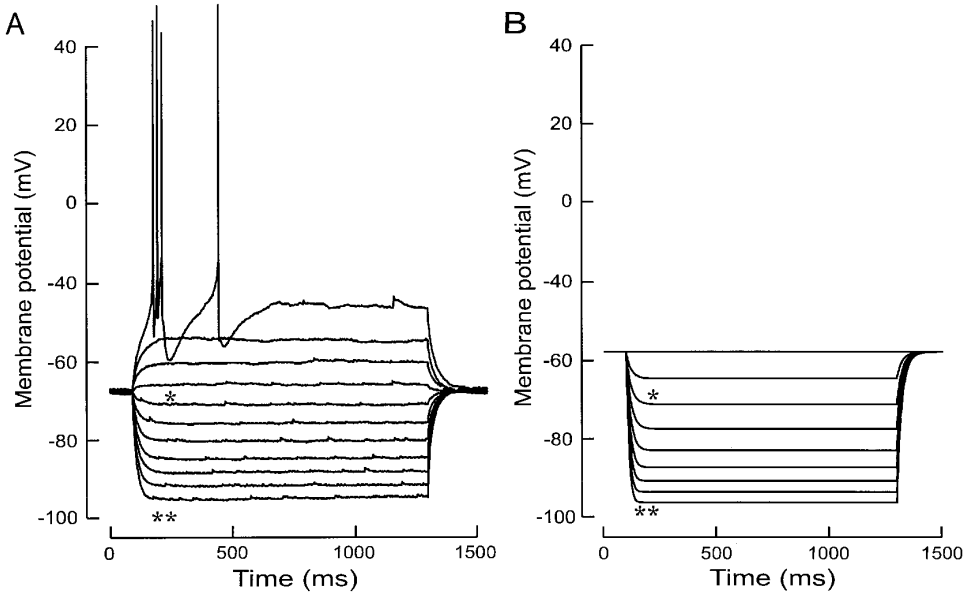

FIG. 2. Responses of an actual *(A)* and simulated *(B)* RE neuron to current injection. In both A and *B*, the amount of current injected during successive traces differs by a fixed increment (30 pA), but the incremental hyperpolarization in response to a fixed increment of current becomes smaller at more hyperpolarized potentials (< -75 mV) and the membrane time constant becomes faster. * Membrane charging curves near −70 mV (time constants were 30 and 21 ms in *A* and *B*, respectively); ** −95 mV (time constants were 16 and 10 ms in *A* and *B*, respectively).

by one parameter, the amount by which g_K was decreased, hereafter denoted ζ, i.e. $g_K(\text{CCK}) = (1 - \zeta)^* g_K(\text{Control})$. Therefore for each condition, we found the summed squared error as a function of ζ ($0 < \zeta < 1$). For each model RE neuron, the optimal ζ and minimal error are presented in Table 2 for CCK agonist suppression of g_K in either all compartments, the somatic compartment only, or the dendritic compartments only.

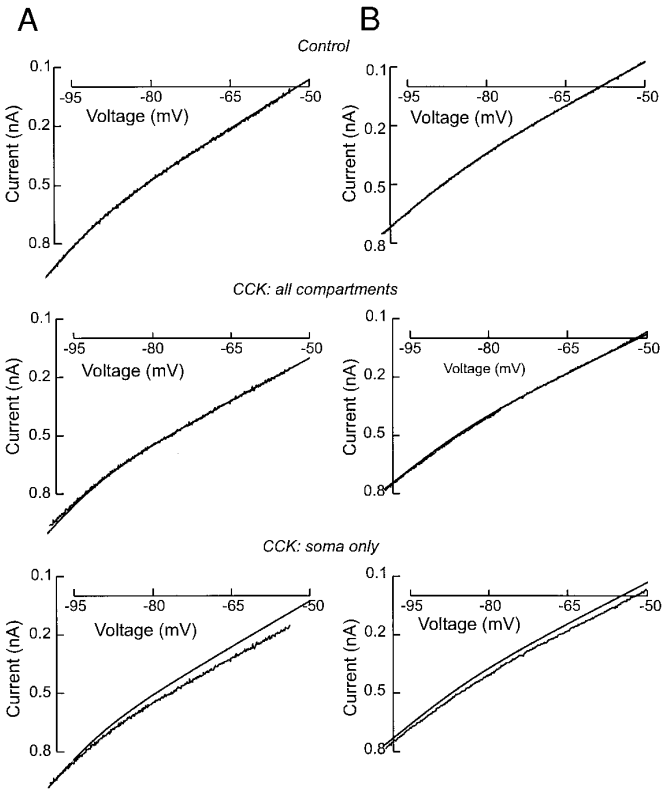

FIG. 3. Comparison of intracellularly recorded (noisy, thicker trace) and simulated (thinner smooth trace) voltage-clamp *I-V* curves in the presence and absence of cholecystokinin (CCK) agonists for RE *neuron 1 (A)* and RE *neuron 2 (B)*. *Top*: Control. Model parameters (leak and I_h) were selected using a simplex algorithm to minimize the difference between simulated and intracellularly recorded curves. *Middle*: CCK, all compartments. Effects of CCK were modeled as uniform suppression (18% in RE *neuron 1* and 22% in RE *neuron 2*) of g_{K+} in all compartments. *Bottom*: CCK, soma only. Model responses could not reproduce experiment results when the effects of CCK were limited to the soma (99% suppression of somatic g_{K^+}).

These results demonstrate that our model requires dendritic CCK effects to accurately simulate the experimentally obtained *I-V* curves. Figure 3*A* (*middle* and *bottom*) compares the experimental *I-V* curve for RE *neuron 1* obtained in the presence of CCK to simulated *I-V* curves for which CCK effects were expressed either in all compartments equally with $\zeta = 0.18$, or only in the soma with $\zeta = 0.99$. Figure 3*B* (*middle* and *bottom*) shows corresponding data for RE *neuron 2*.

To further examine the conditions under which suppression of g_K in model RE neurons can simulate the experimentally observed effects of CCK, we also used the simplex algorithm to select amounts of g_K suppression in each compartment that minimized the difference between the simulated *I-V* curves and the *I-V* curves recorded intracellularly in the presence of CCK. Again, all other parameters had been obtained by simplex fitting of the control *I-V* curves. For both model RE neurons and all initial conditions tested, the simplex algorithm converged to states in which the suppression of g_K, averaged over the proximal and distal dendrites, was as large or larger than the somatic suppression of g_K. This strengthens the conclusion that in our model CCK

TABLE 1. *Model parameters for two RE neurons*

Parameter	*Neuron 1*	*Neuron 2*
G_{leak}	14.3 μS/cm^2	11.9 μS/cm^2
V_{rest}	−52.4 mV	−58.7 mV
G_h	702 μS/cm^2	334 μS/cm^2
E_h	−37.3 mV	−49.8 mV
$V_{1/2}$	−93.2 mV	−87.0 mV
K	5.65 mV	6.06 mV

For each reticular (RE) neuron, the downhill simplex algorithm converged to parameters that produced the best fit to the control [no cholecystokinin (CCK)] *I-V* curve of that cell. Parameters are defined in the text.

TABLE 2. *Localization of CCK effects to dendrites*

	RE *Neuron 1*		RE *Neuron 2*	
	Optimal ζ	Minimal Error	Optimal ζ	Minimal Error
All	0.18	0.017	0.22	0.029
Dendrites only	0.20	0.017	0.24	0.029
Soma only	0.99	0.38	0.99	0.92

For each RE neuron, we simulated varying amounts of g_K suppression and compared the resulting *I-V* curve with the *I-V* curve that had been recorded intracellularly during CCK application. ζ is the fraction by which g_K was suppressed. For each RE neuron, the ζ that produced the best fit to the intracellularly recorded *I-V* curve and the corresponding amount of error are shown for three cases: g_K suppressed in all compartments equally, g_K suppressed in the dendrites only, and g_K suppressed in the soma only. The minimal error is much higher when only somatic g_K is suppressed than in the other two cases, demonstrating that our model requires suppression of dendritic g_K to accurately simulate the effects of CCK observed in vitro.

must suppress dendritic g_K to produce its experimentally observed effects.

Effect of series resistance and I_h

To study effects of the series resistance of the voltage clamp electrode, we compared the reversal potential of the CCK response in our standard model (RE *cell 1* with R_s = 10 MΩ: $E_{CCK} = -125$ mV) to that in models with R_s = 5 MΩ ($E_{CCK} = -116$ mV) and R_s = 20 MΩ ($E_{CCK} < -130$ mV). To determine how I_h affected the reversal potential of the CCK response, we compared *I-V* curves during a simulated voltage ramps of RE *neuron 1* in the presence or absence of I_h (but otherwise identical conditions). The CCK response reversed around −125 mV when we included I_h but around −118 mV when I_h was absent. Thus I_h can significantly hyperpolarize the apparent reversal potential of the CCK response.

DISCUSSION

Relationship to earlier experimental work

Earlier experiments suggested that the CCK agonist, CCK8S, suppresses K^+ conductance in RE neurons but also found that the reversal potential for the CCK8S response was significantly more hyperpolarized than E_K (Cox et al. 1995). The results reported here help to explain these findings by demonstrating that the effects of suppressing passive K^+ conductance may have an apparent reversal potential that is significantly hyperpolarized relative to E_K. Three mechanisms contribute to this apparent hyperpolarization: series resistance of the voltage clamp electrode, effects of CCK8S on dendritic K^+ channels, and I_h in RE neurons.

These three mechanisms all hyperpolarize the reversal potential for the CCK8S response by rendering the voltage clamp less effective, especially at hyperpolarized potentials, so that the actual membrane potential in the vicinity of K^+ channels is more depolarized than the clamp's command voltage. As a result, the actual membrane potential near K^+ channels remains above E_K even when the command voltage reaches E_K. Increasingly hyperpolarized command voltages are required for the membrane potential near K^+ channels to reach E_K. Thus the reversal potential of the CCK8S response appears hyperpolarized.

High series resistance for the voltage-clamp electrode produces a significant voltage difference between the electrode, which is at the command voltage, and the neuron. Thus the membrane potential remains closer to its resting potential and further from the hyperpolarized command. K^+ channels in the dendrites are electrotonically distant from the soma and thus experience a membrane potential that tends to remain close to the resting potential even as the voltage clamp drives the soma to increasingly hyperpolarized potentials. Finally, I_h becomes activated at hyperpolarized membrane potentials, increasing the membrane conductance and opposing further hyperpolarization of the membrane potential.

The standard deviation of E_{CCK} measured experimentally was high (Cox et al. 1995), suggesting that some RE neurons have a reasonable E_{CCK} (i.e. $E_{CCK} \gg E_K$), whereas others do not. This variability may reflect variability in the three factors just discussed, e.g., variable amounts of hyperpolarization-activated current in different RE neurons, different positions of the clamping electrode, etc.

Intracellular recordings from rat locus coeruleus neurons suggest that opiates activate a potassium current, but the experimentally determined reversal potential of the opiate-activated current is hyperpolarized significantly relative to expected E_K (Williams et al. 1988). These results are similar to those of Cox et al. (1995) in many ways. The neurons were inwardly rectifying, ramp *I-V* curves were determined via single-electrode voltage-clamp methodology, and opiate effects were thought to occur through activation of dendritic receptors. Thus the same three factors that we propose hyperpolarize E_{CCK} (inward-rectification, drug actions on K^+ channels in electrotonically distant parts of the cell, and series resistance of the clamping electrode) also could account for the hyperpolarized reversal potential of the opiate-activated current.

Although we attributed the inward rectification of RE neurons to a rapidly activating I_h-type current, any increase in conductance at hyperpolarized potentials would affect E_{CCK} similarly. For example, an inwardly rectifying potassium current would similarly hyperpolarize E_{CCK} in RE neurons.

Could inaccurate estimates of series resistance have altered the results?

We found that suppression of g_K in the dendritic compartments of model RE neurons was necessary to simulate the experimentally observed effects of CCK. However, it is possible that the actual series resistance of the voltage clamp electrode in experiments was not 10 MΩ, as we had assumed, and that had we used the actual value for R_s, our model would have accurately simulated *I-V* curves even when CCK only suppressed g_K in the soma. The following observations suggest that R_s = 10 MΩ was reasonably close to the actual value and that other experimentally reasonable values would not have changed our conclusion about dendritic CCK effects.

First, although we chose values of g_{leak}, V_{rest}, g_h, E_h, $V_{1/2}$, and k to minimize the difference between simulated and intracellularly recorded *I-V* curves in the *absence* of CCK agonist (Fig. 3, *top*), we would not expect the simulated and intracellularly recorded *I-V* curves in the *presence*

of CCK agonist (Fig. 3, *middle*) to be so similar had R_s = 10 MΩ been erroneous. Similarly, although we chose parameters for I_h to simulate *I-V* curves, we would not have expected those parameters also to reproduce accurately the responses of a RE neuron during current injection (Fig. 2) had our R_s estimate been incorrect. Finally, note that R_s = 10 MΩ is an upper bound for the series resistance of the voltage-clamp electrode, and at lower R_s values, the results of simulations in which CCK only affects the soma become even more inconsistent with experimental measurements. This is shown as follows. I_{V_c}, the clamping current injected into the soma, is

$$I_{V_c} = G(V_c - V_m) \quad (3)$$

Where G is a gain factor, V_c is the clamp's command voltage, and V_m is the somatic membrane potential. Comparison of *Eq. 2* with *3* shows that for an ideal voltage-clamp electrode, the effective series resistance, R_s, equals G^{-1}. During voltage-clamp experiments, G varies between 150 and 800 pA/mV, corresponding to R_s values between 1.25 and 6.67 MΩ (although real electrodes have nonnegligible capacitance, we calculate that electrode capacitance would increase effective R_s by <10%). Now in our model, R_s values <10 MΩ produce CCK reversal potentials that are more depolarized than those extrapolated from experimental data, and when CCK only affects the soma, the expected CCK reversal potential becomes even more depolarized. As a result, at R_s values <10 mΩ, the results from simulations in which CCK affects only the soma would become less, not more, consistent with those observed experimentally.

Predictions

In addition to explaining earlier experimental findings (Cox et al. 1995), the results presented here make a prediction about the localization of CCK effects within a neuron. For the biophysical models we have constructed, suppression of g_K in the soma alone is not enough to reproduce the experimentally observed effects of CCK8S. Therefore, we predict that CCK receptors should be present on the dendrites of RE neurons.

Suppression of dendritic g_K in RE neurons could have important functional implications. For example, earlier findings suggest that low-threshold Ca^{2+} channels (T channels) are concentrated in the dendrites of RE neurons (Destexhe et al. 1996). Thus CCK receptors located in the dendrites of RE neurons may be particularly effective at depolarizing the membrane potential in the vicinity of T channels, altering the propensity of RE neurons to burst and thereby affecting intrathalamic oscillations. In other simulations, small depolarizations have been shown to bring RE neurons closer to the burst threshold, strengthening intrathalamic oscillations, whereas larger depolarizations prevent T channels from deinactivating after a burst, shortening intrathalamic oscillations (Sohal and Huguenard, unpublished data). Suppression of g_K near dendritic T channels may enhance these effects and explain why CCK has such potent effects on intrathalamic oscillations in vitro (Cox et al. 1997).

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