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Bistable behaviour in a neocortical neurone model

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INTRACELLULAR recordings have shown that neocortical pyramidal neurones have an intrinsic capacity for regenerative firing. The cellular mechanism of this firing was investigated by computer simulations of a model neurone endowed with standard action potential and persistent sodium (g_{NaP}) conductances. The firing mode of the neurone was determined as a function of leakage and NaP maximal conductances ($\bar{g}_l$ and $\bar{g}_{NaP}$). The neurone had two stable states of activity (bistable) over wide range of $\bar{g}_l$ and $\bar{g}_{NaP}$, one at the resting potential and the other in a regenerative firing mode, that could be triggered by a transient input. This model points to a cellular mechanism that may contribute to the generation and maintenance of long-lasting sustained neuronal discharges in the cerebral cortex.

Key words: Bistability; Hodgkin–Huxley formalism; Neocortex; Persistent sodium conductance

Introduction

Silva *et al.*[1] reported finding 'single-spiking rhythmic' neurons in the neocortex that responded to a 4 ms depolarizing pulse by a sustained discharge lasting up to 20 s in the absence of any excitatory synaptic transmission. This suggests that some cortical neurones have two stable states of activity (bistable behaviour), one silent and the other of continuous activity, that can be triggered by a transient input. This mode of discharge could subserve a variety of temporal processing and coding mechanisms in the brain. In particular, it could account in part for the ability of neurones in the frontal and associative cortices to fire in a highly selective fashion during a delay while an event is memorized, but to be otherwise silent.[2,3]

Single neurones displaying a bistable behaviour have been found in invertebrates.[4] These patterns are the result of the molecular properties of neurones themselves (repertoire of ionic channels) and of the connectivity of local networks (recurrent loops). The cellular mechanisms underlying the bistable behaviour of neocortical neurones are unknown. Sustained temporal patterns can appear as a solution of coupled non-linear differential equations.[5] These patterns may thus be produced by interactions between membrane ion channels.[6] Experimental and theoretical evidence suggests that a persistent sodium current dominates the excitability of pyramidal neocortical neurones at membrane potentials below the action potential threshold,[7] and contributes to subthreshold oscillations and repetitive firing behaviour.[8–10] The goal of the present study was to determine whether a single neurone endowed with action potential and persistent sodium conductances could display a bistable behaviour. We explored the role of g_{NaP} in the generation and maintenance of regenerative discharge in a model of a cortical pyramidal cell. This was done by analysing the firing mode of the neurone model in response to a transient input as a function of the membrane time constant and NaP maximal conductance.

Materials and Methods

This paper presents the simulations of an isopotential model neurone which includes the sodium and potassium currents of the action potential, a persistent sodium current, a leakage current and an injected current. The membrane potential V_m obeyed the following equation:

$$C_m \frac{dV_m}{dt} = \bar{g}_{Na} m^3 h (V_{Na} - V_m) + \bar{g}_K n^4 (V_K - V_m) + \bar{g}_{NaP} m_{NaP} (V_{NaP} - V_m) + \bar{g}_l (V_l - V_m) + I_{inj}$$

where $C_m = 1\ \mu F\ cm^{-2}$ and $V_l = -71.5$ mV. The notation $\bar{g}$ designates maximal conductances. The leakage conductance ($\bar{g}_l$) was assumed to be in the range 0.02–0.2 mS cm^{-2}. This ensured that the corre-

sponding passive time constant (τ_m) lies between 5 and 50 ms, a range covering the various physiological estimations made in neocortical pyramidal neurons.[11,12]

The description of the active conductances of the model used the Hodgkin–Huxley formalism. The evolution of the gating particles *m, h, n* followed first-order kinetics.

$$\frac{dx}{dt} = \alpha_x(V_m)(1-x) - \beta_x(V_m)x,\ x = m,h,n$$

Rates of activation and inactivation of fast sodium conductance:

$$\alpha_m(V_m) = \frac{0.55(V_m + 45.5)}{1 - \exp\left(\frac{-45.5 - V_m}{4}\right)}$$

$$\alpha_h(V_m) = 0.115 \exp\left(\frac{-V_m - 48}{18}\right)$$

$$\beta_m(V_m) = \frac{0.44(V_m + 18.5)}{\exp\left(\frac{V_m + 18.5}{5}\right) - 1}$$

$$\beta_h(V_m) = \frac{3.6}{1 + \exp\left(\frac{-V_m - 25}{5}\right)}$$

and rates of activation of fast potassium conductance:

$$\alpha_n(V_m) = \frac{0.0178(-50 - V_m)}{\exp\left(\frac{-50 - V_m}{5}\right) - 1}$$

$$\beta_n(V_m) = 0.28 \exp\left(\frac{-55 - V_m}{40}\right)$$

were derived from Ref. 13. The maximal conductances and the rate functions were scaled to reproduce typical action potential characteristics of regular spiking cortical neurons:[14–16] height ~80 mV, duration ~1 ms, rate of rise ~350 mV ms^{-1}, rate of fall ~ –80 mV ms^{-1}. The following values were used for all simulations: $\bar{g}_{Na}$ = 20 mS cm^{-2}, $\bar{g}_K$ = 2 mS cm^{-2}, V_{Na} = 45 mV, V_K = –85 mV.

The persistent sodium conductance activation followed

$$\frac{dm_{NaP}}{dt} = \frac{m^{\infty}_{NaP}(V_m) - m_{NaP}}{\tau_{NaP}(V_m)}$$

The voltage-dependence of m^{∞}_{NaP} was taken from Ref. 17 (Fig. 1A)

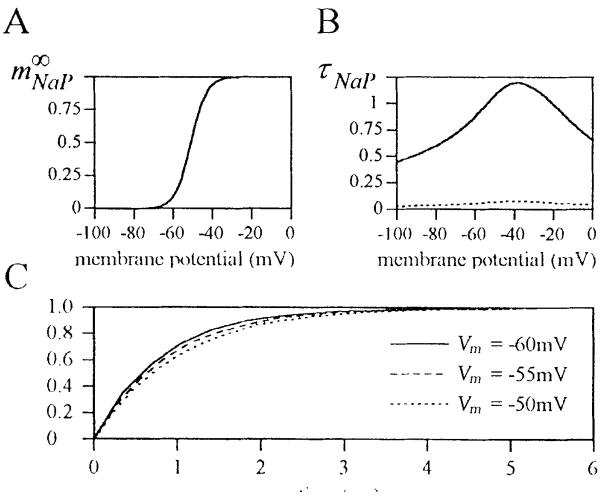

FIG. 1. The persistent sodium (NaP) conductance model. (**A**) Steady-state activation function. (**B**) Activation time constants of the fast (dotted line) and persistent (solid line) sodium conductances. (**C**) NaP kinetics were scaled from fast sodium kinetics so that the NaP current reached 95% of its maximal value within 2–4 ms under voltage-clamp at subthreshold potentials. Currents are normalized.

$$m^{\infty}_{NaP}(V_m) = \frac{1}{1 + \exp\left(\frac{-51 - V_m}{4}\right)}$$

The kinetics of activation of g_{NaP} are now known precisely. The persistent sodium current reaches its steady-state value within 2–4 ms in the subthreshold voltage range in neocortical neurones.[18] We assumed a simple model of g_{NaP} kinetics which consisted of a scaled version of g_{Na} kinetics (Fig. 1B)

$$\tau_{NaP} = \left[\left(\frac{0.0333(V_m + 45.5)}{1 - \exp\left(\frac{-45.5 - V_m}{4}\right)}\right) + \left(\frac{0.0271(V_m + 18.5)}{\exp\left(\frac{V_m + 18.5}{5}\right) - 1}\right)\right]^{-1}$$

The time constant was fitted so that in a reduced $\bar{g}_l/\bar{g}_{NaP}$ model, the persistent sodium current reached 95% of its steady-state amplitude in 2–4 ms under voltage-clamp in the subthreshold range (Fig. 1C). The persistent sodium maximal conductance ($\bar{g}_{NaP}$) was assumed to be in the range 0–0.3 mS cm^{-2} (i.e. 0–1.5% of $\bar{g}_{Na}$).[19,20] V_{NaP} was 45 mV.

The firing threshold was determined as the maximal observable steady-state potential when the intensity of a 500 ms current step was raised.

The simulations began with activation and inactivation at their steady-state values at resting potential when it existed, otherwise at –71.5 mV.

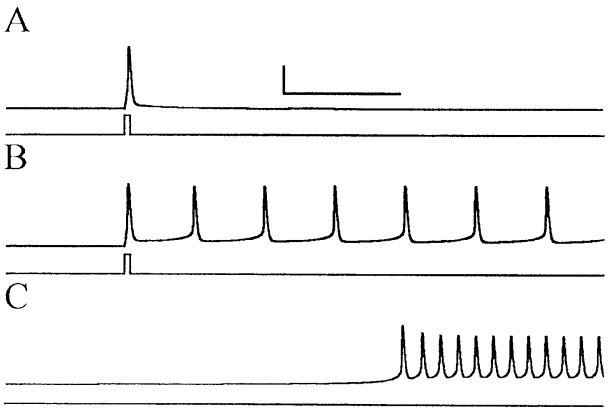

FIG. 2. The firing modes of the model neurone: transient (**A**), sustained (**B**), spontaneous sustained (**C**). The leakage conductance $\bar{g}_l$ was 0.05 mS cm^{-2} $\bar{g}_{NaP}$ was 0 (A), 0.07 mS cm^{-2} (B), 0.12 mS cm^{-2} (C). The injected current is shown below each trace: 30 μA cm^{-2} for 1 ms (not to scale) in (A,B), no injected current in (C). Simulated time is 250 ms. The first 100 ms of simulation is truncated in (C). Scale bars (50 ms, 50 mV) apply to all traces.

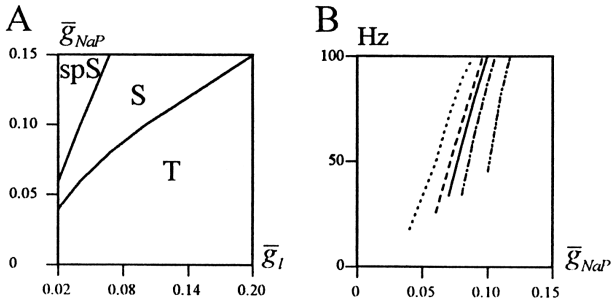

FIG. 3. (**A**) The three domains of discharge in the ($\bar{g}_l$, $\bar{g}_{NaP}$) plane. The borders are defined by the existence of a resting potential (spS/S) and the nature of the discharge triggered by the injection of a threshold current (T/S). (**B**) The firing frequency depends on $\bar{g}_{NaP}$ and $\bar{g}_l$. The stabilized frequency was 0 Hz in the T domain. The frequency in the S and spS domain increased with $\bar{g}_{NaP}$, from a minimal non-zero value (20–40 Hz, see Results) and decreased with $\bar{g}_l$ (0.02 mS cm^{-2}, dotted line; 0.04 mS cm^{-2}, dashed line; 0.05 mS cm^{-2}, solid line; 0.067 mS cm^{-2}, dotted-dash line; 0.1 mS cm^{-2}, double dotted-dash line).

Results

The model was first tested with $\bar{g}_l = 0.05$ mS cm^{-2} ($\tau_m = 20$ ms). When the persistent sodium conductance was not included in the model neurone ($\bar{g}_{NaP} = 0$) the resting potential was –71.5 mV. The firing threshold was ~ –53 mV. Injection of a threshold current ($I_{inj} = 30$ μA cm^{-2}, 1 ms) elicited a single action potential (Fig. 2A). With $\bar{g}_{NaP} = 0.07$ mS cm^{-2}, the resting potential was about –70.3 mV (firing threshold ~ –66 mV), but injection of the same threshold current induced a stable rhythmic (34 Hz) self-regenerative discharge (Fig. 2B). Thus the neurone was bistable. The neurone was found to have a spontaneous regenerative (pacemaker) discharge for $\bar{g}_{NaP} = 0.12$ mS cm^{-2} (Fig. 2C). These three types of behaviour were called transient (T), sustained (S), and spontaneous sustained (spS) activity. These results, as well as those reported below, did not depend upon the amplitude of the injected suprathreshold current. At higher values of $\bar{g}_{NaP}$ (>0.15 mS cm^{-2}), the size of the spikes decreased below the lower limit of physiological observations (<70 mV). Beyond $\bar{g}_{NaP} = 0.2$ mS cm^{-2}, the response of the neurone was saturated, i.e. no spike was observed.

We tested the robustness of these observations for different values of the passive time constant (see Materials and Methods). The value of the leakage conductance was therefore systematically varied. The domains corresponding to the three modes of discharge are shown in the ($\bar{g}_l$, $\bar{g}_{NaP}$) plane (Fig.3A). The domains were found to be large and separated by smooth borders.

We calculated the spiking frequency of the neurone (Fig. 3B). In the T domain, the neurone emitted spikes in a finite time window defined by $\bar{g}_{NaP}$. Its spiking frequency was taken as zero. In the S domain, the spiking frequency increased monotonically with $\bar{g}_{NaP}$ for any $\bar{g}_l$, and decreased with $\bar{g}_l$ for any $\bar{g}_{NaP}$. The discretization step of $\bar{g}_{NaP}$ was ~5% of the physiological range considered (0–0.15 mS cm^{-2}). If we assume that this corresponds to the maximal accuracy of the regulation of $\bar{g}_{NaP}$, a minimal frequency can be estimated as a function of $\bar{g}_l$ and was found to be 20–40 Hz (Fig. 3B).

Figure 4 shows the changes in membrane potential (Fig. 4A, 4B), the fast sodium conductance (Fig. 4C, 4D), and the persistent sodium conductance (Fig. 4E, 4F) of the T ($\bar{g}_{NaP} = 0.06$ mS cm^{-2}) and S ($\bar{g}_{NaP} = 0.07$ mS cm^{-2}) domains ($\bar{g}_l = 0.05$ mS cm^{-2}) in response to the same threshold input. The persistent sodium conductance remained activated during repolarization of the membrane potential (compare Fig. 4C with E and Fig. 4D with F). In the S domain, the NaP conductance remained substantial during interspike intervals. It depolarized the membrane up to the action potential threshold, allowing for the generation of new spikes (Fig. 4F).

A typical S neurone had a resting potential about –70 mV (i.e. an equivalent *in vitro* condition) and displayed a bistable behaviour ($\bar{g}_l = 0.05$ mS cm^{-2}; $\bar{g}_{NaP} = 0.07$ mS cm^{-2}). The question arises of whether a similar behaviour could be observed in a neurone with a more depolarized steady-state potential (i.e. an equivalent *in vivo* condition). A bistable behaviour was actually observed when a constant current was injected (0.145 μA cm^{-2}) to maintain a steady membrane potential of ~–65 mV: a transient current (30 μA cm^{-2}, 1 ms) elicited a stable rhythmic discharge at 25 Hz. In this case, a lower value of $\bar{g}_{NaP}$ was required (0.057 mS cm^{-2}).

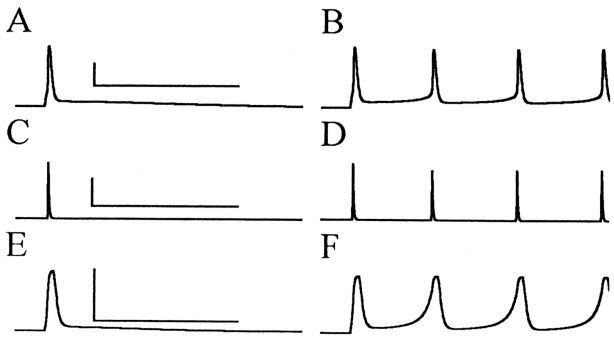

FIG. 4. Membrane potential (**A**,**B**), fast sodium conductance (**C**,**D**), and persistent sodium conductance (**E**,**F**) of the transient (left traces, $\bar{g}_{NaP}$ = 0.06 mS cm^{-2}) and sustained discharges (right traces, $\bar{g}_{NaP}$ = 0.07 mS cm^{-2}). $\bar{g}_l$ was 0.05 mS cm^{-2}. Simulated time is 100 ms. Scale bars correspond to 50 ms (all traces), 50 mV (A,B), 5 mS cm^{-2} (C,D), and 0.05 mS cm^{-2} (E,F).

Discussion

This study shows that a model neurone endowed with neocortical pyramidal action potential and persistent sodium conductances can exhibit bistable behaviour. The neurone had a resting potential over large range of leakage ($\bar{g}_l$) and NaP maximal ($\bar{g}_{NaP}$) conductances, and the value of $\bar{g}_{NaP}$ indicated whether the response to a brief input was transient (T domain), or sustained (S domain). Spontaneous discharges were observed for low $\bar{g}_l$ and high $\bar{g}_{NaP}$ (spS domain).

A persistent sodium conductance is responsible for inward rectification in neocortical neurones, and contributes to their excitability, amplification of synaptic inputs, and subthreshold membrane oscillations.[21] Our results show that this persistent sodium conductance may also be part of an intrinsic mechanism of regenerative spiking. This mechanism is based on the strong activation of NaP in the range of –60/–50 mV. Our neurone model is a simplified isopotential model and does not incorporate several intrinsic properties that could interact with the mechanism described here. Any direct or rebound depolarizing current (calcium currents,[22] I_h current,[23] dendritic voltage reflection) would favour sustained firing. Conversely, voltage- or calcium-activated potassium outward currents would reduce the firing frequency or break the regenerative process by repolarizing the membrane below the range where NaP is active. Hence, neither the conditions of bistability nor the firing frequency of the sustained discharge should be considered to be absolute estimates.

The S domain neurones in our simulations resemble the single-spiking rhythmic neurones found by Silva *et al.*[1] in neocortical layer V. Our model reproduces two striking features of these rhythmic neurones: (1) these neurones have a lower firing threshold than the classical regular spiking neurones; (2) they display a bistable behaviour when a constant current is injected. Silva *et al.*[1] suggested that the bistability was based on sodium current. However, the role of sodium conductances was assessed by the specific sodium channel antagonist TTX, which antagonizes both fast and persistent sodium conductances.[1] The question arises of whether the persistent Na current is necessary for the existence of a bistable behaviour. Guckenheimer and Labouriau[6] showed the existence of a bistable behaviour in the classical Hodgkin–Huxley equations for action potential in the squid axon. This solution corresponded, however, to a small region of the parameter space and required the potassium equilibrium potential to be higher than the physiological value in the mammalian cortex. Numerical simulations failed to reveal any bistable behaviour in our model of the pyramidal neurone with $\bar{g}_{NaP} = 0$ in a large range of $\bar{g}_{Na}$ and $\bar{g}_K$ and for a typical value of V_K (–85 mV).

Other inward currents could lead to such a regenerative mechanism. The 'long' calcium current is a candidate, because it is non-inactivating.[22] However, it is not activated at subthreshold potentials since its threshold is high (–30 mV). The 'transient' calcium current is activated at subthreshold potentials, but inactivates rapidly. It has been suggested that the I_h current participates in rhythmic firing.[22] It does not appear to be a good candidate for bistability, however, because of the reversed shape of its steady-state activation function. These observations, and the fact that the bistable mode of discharge appeared over the wide range of usual passive time constants and for values of $\bar{g}_{NaP}$ in agreement with physiological estimations, point to the involvement of the persistent sodium conductance in regenerative firing in neocortical cells. The prediction of the model could be tested experimentally using a specific antagonist of the persistent sodium current.[24]

In a bistable neurone, the transition between rest and regenerative discharge elicited by a transient synaptic input defines a temporal trace of this input. Neuronal traces of a memorized event lie in sustained discharges of prefrontal cortical neurones of animals performing short-term memory tasks.[2,3] The present model indicates a cellular mechanisms that may contribute to these memory-related activities. This mechanism is relevant, since the NaP conductance strongly influences the membrane excitability of prefrontal neurones and is modulated by dopamine,[25] which is crucial for short-term memory processes.[3]

Conclusion

This model describes a cellular mechanism for the generation and maintenance of long-lasting sustained

neuronal discharges in the cerebral cortex. This intrinsic mechanism could act, together with recurrent connections, to maintain elevated firing rates over a period that is longer than a stimulating input. Neuromodulation of this mechanism by dopamine could help explaining the relationship between physiological and behavioural aspects of short-term working memory processes.

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General Summary
We have investigated the role of a persistent sodium conductance in the generation and maintenance of an intrinsic regenerative discharge in a model of a neocortical pyramidal neurone. The model neurone displayed a bistable behaviour over a wide range of leakage and persistent sodium maximal conductances; it had a stable resting potential and entered a regenerative firing mode for a transient input. The bistable behaviour of cortical neurones may be one method of generating the memory-related activities that occur in the frontal lobe of animals during the performance of short-term memory tasks.