



ACTION POTENTIAL THRESHOLD OF HIPPOCAMPAL PYRAMIDAL CELLS *IN VIVO* IS INCREASED BY RECENT SPIKING ACTIVITY

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Abstract—Understanding the mechanisms that influence the initiation of action potentials in single neurons is an important step in determining the way information is processed by neural networks. Therefore, we have investigated the properties of action potential thresholds for hippocampal neurons using *in vivo* intracellular recording methods in Sprague–Dawley rats. The use of *in vivo* recording has the advantage of the presence of naturally occurring spatio-temporal patterns of synaptic activity which lead to action potential initiation. We have found there is a large variability in the threshold voltage (5.7 ± 1.7 mV; $n = 22$) of individual action potentials. We have identified two separate factors that contribute to this variation in threshold: (1) fast rates of membrane potential change prior to the action potential are associated with more hyperpolarized thresholds (increased excitability) and (2) the occurrence of other action potentials in the 1 s prior to any given action potential is associated with more depolarized thresholds (decreased excitability).

We suggest that prior action potentials cause sodium channel inactivation that recovers with approximately a 1-s time constant and thus depresses action potential threshold during this period. © 2001 IBRO. Published by Elsevier Science Ltd. All rights reserved.

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Understanding the mechanisms that lead to action potential initiation in single cells is a necessary step in determining the way neural networks process information. In particular, the precise mechanisms that underlie the initiation of action potentials are important factors for understanding whether information is processed using a rate or temporal code. A rate code implies that the mean firing rate of a neuron in a given period of time carries all the relevant information and the timing of individual action potentials is irrelevant. In contrast, a temporal code implies that the specific timing of each individual action potential carries critical information. It has been observed that the firing patterns of cortical neurons are more irregular than necessary to convey a simple rate code. As a result, it has been suggested that the irregularity is indicative of temporal coding. Many recent computational and experimental studies have tried to understand the source of the firing pattern irregularity of cortical neurons. Two sources for the firing pattern variability have been considered: (1) the specific properties of the synaptic input and (2) the intrinsic properties of the neuron. A number of experimental and computational modeling studies have concluded that synchrony between individual components of the synaptic inputs is

necessary to account for the variability in the firing patterns. In contrast, other computational studies have suggested that the intrinsic properties of cortical neurons may account for some of the variability. These intrinsic properties include non-linear properties of dendrites (Softky and Koch, 1993), the presence of a relative refractory period following action potentials (Troyer and Miller, 1997), the relationship between membrane time constant and threshold (Kempster et al., 1998) and the dynamical properties of the neuronal membrane (Gutkin and Ermentrout, 1998).

Here we have examined factors which influence the threshold voltage of action potentials of CA1 pyramidal cells *in vivo*. Significant variations in action potential threshold would have implications for the precise timing of action potentials since the probability of initiating an action potential could not be predicted by only fluctuations in the membrane potential. Portions of this work have been presented previously (Henze et al., 1999).

EXPERIMENTAL PROCEDURES

Nineteen rats (350–450 g) of the Sprague–Dawley strain (Hill-top Labs, Scottsdale, PA, USA) were anesthetized with urethane (1.5 g/kg; Sigma, St. Louis, MO, USA) and placed in a stereotaxic apparatus. The body temperature of the rat was kept constant by a small animal thermoregulation device. The scalp was removed and a small (1.2 × 1.2 mm) bone window was drilled above the hippocampus (centered at anterior–posterior = −3.5 and lateral = 2.5 mm from bregma) for extra- and intracellular recordings. A pair of stimulating electrodes (100 μm each, with 0.5-mm tip separation) were inserted into the left fimbria-fornix (anterior–posterior = −1.3, lateral = 1.0, ventral = 3.95) to stimu-

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Abbreviations: Ih or H-current, hyperpolarization-activated cationic current; ISI, inter-spike interval.

(2) the action potential had a distinct afterhyperpolarization. Previous work has demonstrated that these criteria successfully identify somatic recordings *in vivo* (Kamondi et al., 1998). The passive and action potential properties of the neurons are summarized in Table 1. For individual cells, the threshold voltage for action potential initiation was not constant across individual action potentials during a recording epoch (Figs. 2A, B, 3A and 4A). In addition, we noticed that the membrane potential between action potentials could occasionally exceed the minimum threshold voltage observed for that cell without initiating an action potential (Fig. 2A, C).

The variation in action potential threshold could arise from a variety of sources. Previous work has demonstrated that the rate of change of the membrane potential

just prior to the action potential plays an important role in action potential initiation (Bryant and Segundo, 1976; Wickens and Wilson, 1998; Azouz and Gray, 1999, 2000). Similar to these previous studies, we found that action potential threshold for CA1 pyramidal cells is affected by the rate of membrane potential change just prior to the action potential. Examination of the period prior to action potentials indicated that the 10 ms prior to action potential threshold consisted of a depolarizing upward deflection in the membrane potential. This depolarizing deflection is most likely due to synaptic input. Figure 3 shows the relationship between the slopes of linear fits to the 10 ms preceding each action potential to the action potential threshold for each cell. Overall, there was a significant relationship between the rate of

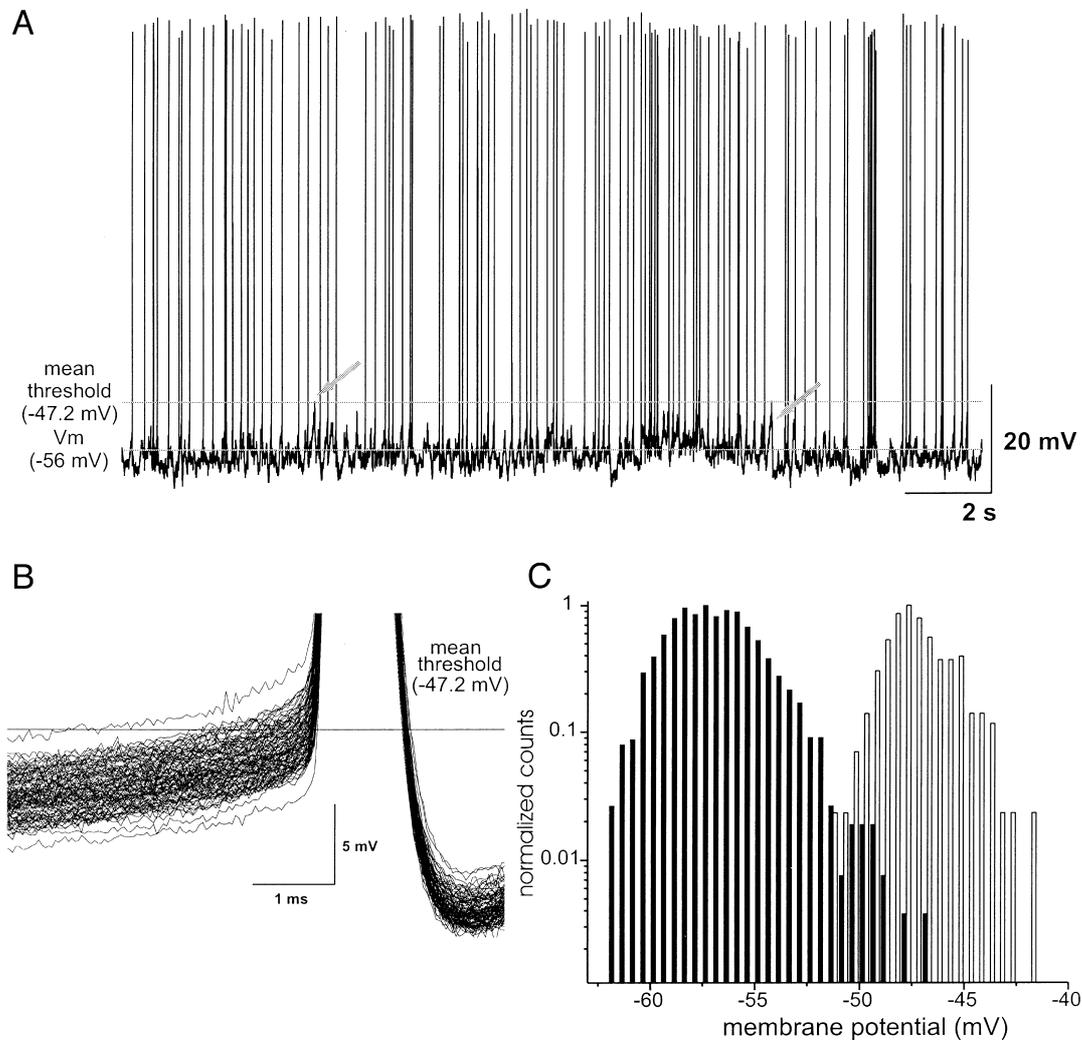


Fig. 2. Variation of CA1 pyramidal cell action potential threshold *in vivo*. (A) Twenty seconds of spontaneous action potentials at resting membrane potential (-56 mV). Arrows indicate two occasions when the membrane potential approached the mean action potential threshold (-47.2 mV indicated by horizontal line) without initiating an action potential. (B) All of the action potentials from A showing the variation in the threshold of the action potentials. (C) A normalized histogram of local peak membrane potential between action potentials (solid bars) and action potential thresholds (open bars) on a log scale from 50 s of data. The between action potential values are local maxima for consecutive 10 ms periods starting from the previous action potential's AHP and excluding the 50 ms prior to each action potential. Notice that there is a distinct overlap between the two distributions indicating that pyramidal cells do not have a simple voltage threshold.

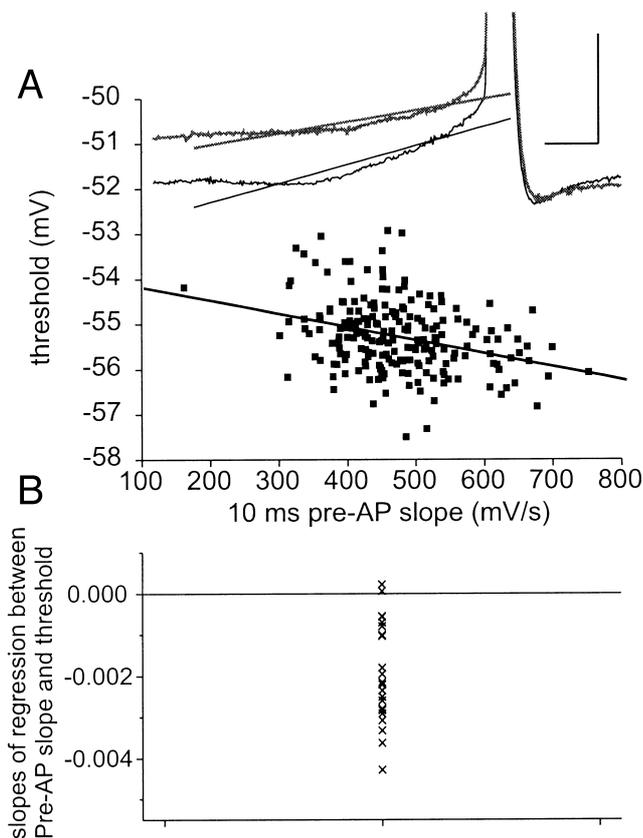


Fig. 3. The rate of membrane potential change is negatively correlated with action potential (AP) threshold. (A) Plot of the slope of action potential threshold versus the membrane potential change over the 10 ms preceding each action potential for a single cell. The line is the best-fit line. Inset: Example of how the data plotted in A was obtained. For each action potential, a best-fit line was fit to the 10 ms preceding the threshold. A slow (upper) and fast (lower) membrane potential change prior to an action potential is shown with their respective best-fit lines. (B) Summary data from all 22 cells. Each point represents the slopes of the regression lines between the action potential threshold and the slope of the 10 ms pre-action potential membrane potential for a single cell. Almost all the regression slopes were negative and overall there was a significant relationship between threshold and the rate of pre-action potential membrane potential change ($P < 0.0001$, two-tailed t -test against zero; $n = 22$).

membrane potential change and threshold, with faster changes leading to lower thresholds ($P < 0.0001$; $n = 22$ cells).

We considered additional factors that might also contribute to the action potential threshold variability. Previous modeling studies suggested that, at least for short intervals, time-since-last-spike, or ISI, could influence the occurrence of subsequent spikes (Troyer and Miller, 1997) due to the potassium channel-mediated refractory period. Therefore, we looked for an influence of previous ISI on action potential threshold. Epochs of firing (38–300 s) were selected for analysis based upon having less than a 1-mV change in the mean membrane potential over the epoch and a sufficient number of action potentials for regression analysis. This selection process ensured that slow shifts in electrode drift or membrane potential did not confound our studies. Figure 4A shows the measured thresholds for individual action potentials as a function of time during a 3-min recording period. We found that the action potential threshold was negatively correlated with the log of the time since the last action potential (Fig. 4B). Surprisingly, the threshold of

any given action potential was increased by other action potentials that occur even as long ago as 1 s.

A simple hypothesis to account for these observations is that each action potential results in the activation or inactivation of intrinsic voltage-gated conductances that recover with a relatively long time constant. If this hypothesis is true then it is possible that more than one previous action potential could be modulating initiation of any given action potential. We tested this possibility by applying a partial regression analysis on multiple previous ISIs. Figure 5A illustrates the question posed by the partial regression analysis. The analysis explicitly asks how much of the variability in the threshold of a single action potential (arrow) can be accounted for by 1st, 2nd, ..., n th previous ISI. We found that action potential threshold in many cells was partially correlated with multiple previous ISIs (see Experimental procedures). The results from all 22 cells are shown in Fig. 5B. Further examination revealed that the number of significantly correlated previous ISIs for a given cell was related to the mean firing rate of the cell. This relationship could occur for two reasons: (1) the number of

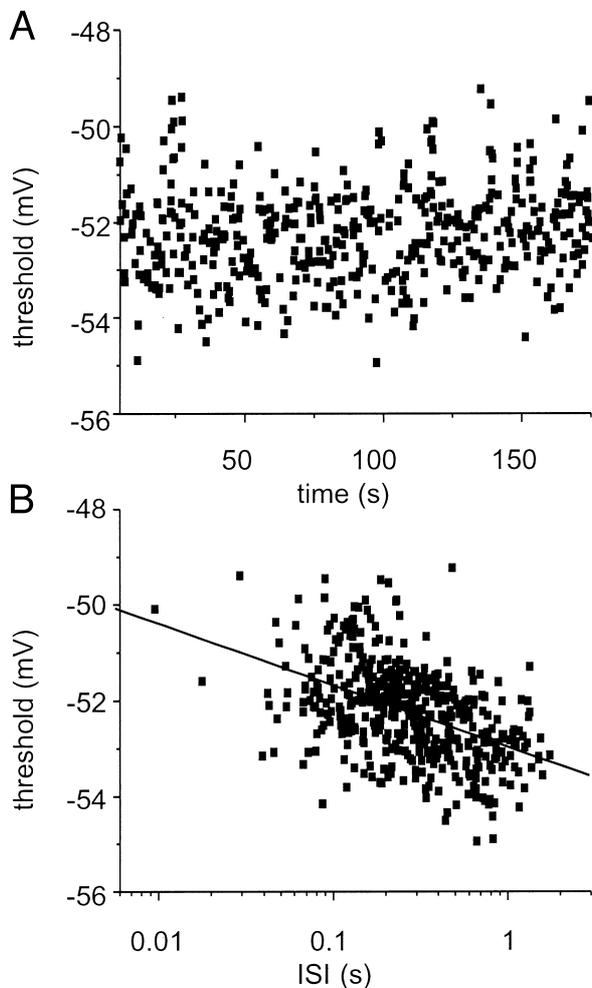


Fig. 4. Action potential threshold and maximum rising slope varies as a function of time elapsed since the last action potential. (A) Action potential threshold values from a single neuron for a 170-s period showing there was no general drift in the threshold. (B) The threshold values from A plotted versus the log of the time since the last action potential. The best-fit line is also shown ($R = -0.47$, $P < 0.0001$, $n = 467$ action potentials).

action potentials in a fixed amount of time before any given action potential influences the threshold for that action potential or (2) the average membrane potential controls both the firing rate and the mean threshold. However, there was no significant correlation between the average membrane potential and the mean ISI across cells ($P > 0.8$; data not shown). Therefore, the duration of prior time when action potentials can influence the threshold can be derived by taking the product of the number of significant regression steps and the mean ISI for each cell. The mean amount of prior time when prior action potentials can influence an action potential is 1.1 ± 0.2 s (\pm S.E.M.). Similar results were obtained in one CA3 pyramidal cell and two hilar mossy cells.

The data presented above suggest that previous action potentials inhibit subsequent action potentials by raising the threshold for action potential initiation. This elevated threshold then decays as a function of time back to some baseline level. If the mechanism behind this threshold

inhibition is due to modulation of intrinsic voltage-gated conductances, then manipulation of the membrane potential between action potentials is expected to influence the threshold of subsequent action potentials. We tested this hypothesis by triggering hyperpolarizing current injections (0.1–2 nA for 60 ms) immediately following spontaneous action potentials. Figure 6A shows a spontaneous train of action potentials followed by triggered hyperpolarizations. Figure 6B shows a single action potential-hyperpolarization event. Similar to Fig. 4, threshold versus log ISI shows a negative correlation (Fig. 6C). However, when each action potential was followed by a strong hyperpolarization the correlation between threshold and ISI was reversed (Fig. 6D). Figure 7 summarizes the results from the nine cells when trailing hyperpolarizations were applied. The trailing hyperpolarizations decreased or reversed the mean slope of the relationship between the threshold and log ISI, -0.30 ± 0.03 and 0.28 ± 0.13 (\pm S.E.M.; $P < 0.002$; paired *t*-test) for control and hyperpolarization, respectively. Therefore, we conclude that action-potential-dependent modulation of voltage-gated conductances is the mechanism which underlies the ISI dependence of action potential threshold.

There are three general candidates for an intrinsic conductance mediating this phenomenon. One possible mechanism underlying the effect of ISI on threshold could be due to the slow recovery of sodium channels from inactivation (Colbert et al., 1997; Jung et al., 1997; Mickus et al., 1999). Alternatively, it is possible that action potentials deactivate the hyperpolarization-activated cationic current I_h (or H-current) and the trailing hyperpolarization reactivates the H-current. However, in CA1 pyramidal cells the H-current time constant of deactivation is too long (18 ms) and the time constant of activation is too short (17 ms; Magee, 1998) to explain the effect of single action potentials on the threshold of other action potentials up to 1 s later. In addition, the H-current is mostly deactivated at the mean membrane potential used during our analysis (-60.1 mV). Finally, it is possible that some slowly inactivating potassium channel is recruited by action potentials which serves to increase the threshold of subsequent action potentials. If the mechanism is due to a potassium channel it must have properties such that it is rapidly activated by single action potentials and is slowly inactivated/deactivated around resting membrane potential. Furthermore, it must be rapidly deactivated/inactivated by brief strong hyperpolarization. We are not aware of any known potassium channels that meet these requirements. Therefore we favor the hypothesis that sodium channel inactivation underlies the observations. Further support for a sodium-channel-dependent mechanism comes from examination of the maximum slope of the rising phase of the action potential. It is known that the upstroke of the action potential is dominated by the sodium channel currents. Figure 6E shows that the maximum rising slope linearly increases as a function of log ISI, consistent with the slow recovery of sodium channels from inactivation. The same partial regression analysis that was performed on the threshold

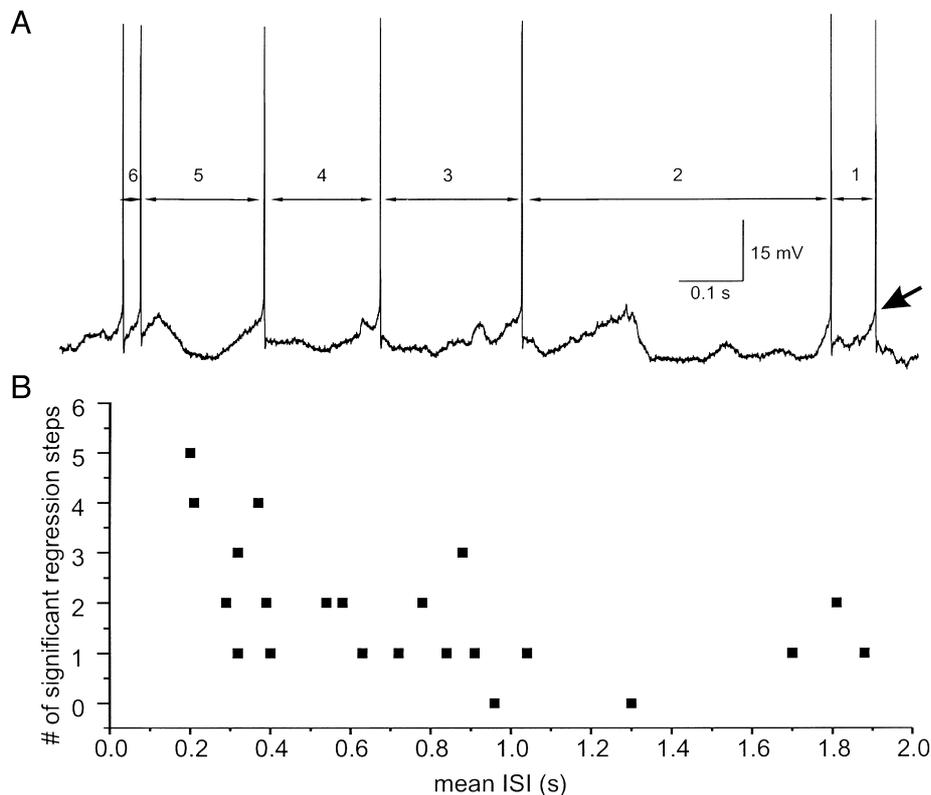


Fig. 5. Action potential threshold depends on the occurrence of multiple previous action potentials. (A) Example illustrating the concept of how the threshold of a single action potential depends on the ISIs of multiple previous action potentials. For this cell, it was found that the threshold of any particular action potential (arrow) is influenced by six previous ISIs. (B) Summary results from 22 CA1 pyramidal cells recorded for this study. The number of significant partial regression steps ($P > 0.05$) versus the mean ISI for each cell is plotted. The values obtained by regressing on thresholds are shown for all 22 cells.

was done for the maximum rising slope for all 22 cells. This analysis revealed that the maximum rising slope is even more sensitive to previous action potentials and is influenced by any action potentials in the previous 1.8 ± 0.2 s (\pm S.E.M.) versus the 1.1 ± 0.2 s (\pm S.E.M.) calculated for threshold ($P < 0.01$, students paired t -test). Furthermore, the trailing hyperpolarization protocol reverses the mean regression slope of the rising slope–ISI relationship [Figs. 6F and 7B; 5.10 ± 0.6 and -0.82 ± 1.46 (\pm S.E.M.; $P < 0.004$; paired t -test)] for control and hyperpolarization, respectively. This is expected since hyperpolarization is known to facilitate the recovery of sodium channels from inactivation (Mickus et al., 1999).

DISCUSSION

We have shown that the voltage threshold of action potentials of hippocampal CA1 pyramidal cells *in vivo* varies during the course of firing activity evoked by spontaneous synaptic input. We have also shown that at least a portion of the threshold variance is accounted for by both the rate of membrane potential change prior to the action potential as well as the occurrence of action potentials in the previous 1 s. We propose that the effect of previous action potentials on subsequent action poten-

tials can be attributed to the voltage-dependent properties of sodium channels.

Technical considerations

Although we find that CA1 pyramidal cells have an action potential threshold that has a mean range of almost 6 mV, it must be remembered that intracellular membrane potential measured against a distant reference is the sum of the actual transmembrane potential and the local field potential. As a result, the absolute values of the threshold range may be smaller than reported in this dataset. However, the extracellular field potential rarely varies by more than 0.5 mV in the pyramidal layer of CA1 (Buzsáki et al., 1983) and therefore is not expected to account for all the variance. The observation that at least a portion of the variance in the threshold can be accounted for by the occurrence of previous action potentials indicates that some portion of the threshold variance is independent of the extracellular field potentials. This conclusion is further supported by the observation that the trailing hyperpolarizations alter the threshold–ISI relationship.

Another potential caveat concerns whether or not we are recording the voltage from the region of the cell where the action potential is initiated. If the action potential were to be initiated at some location remote

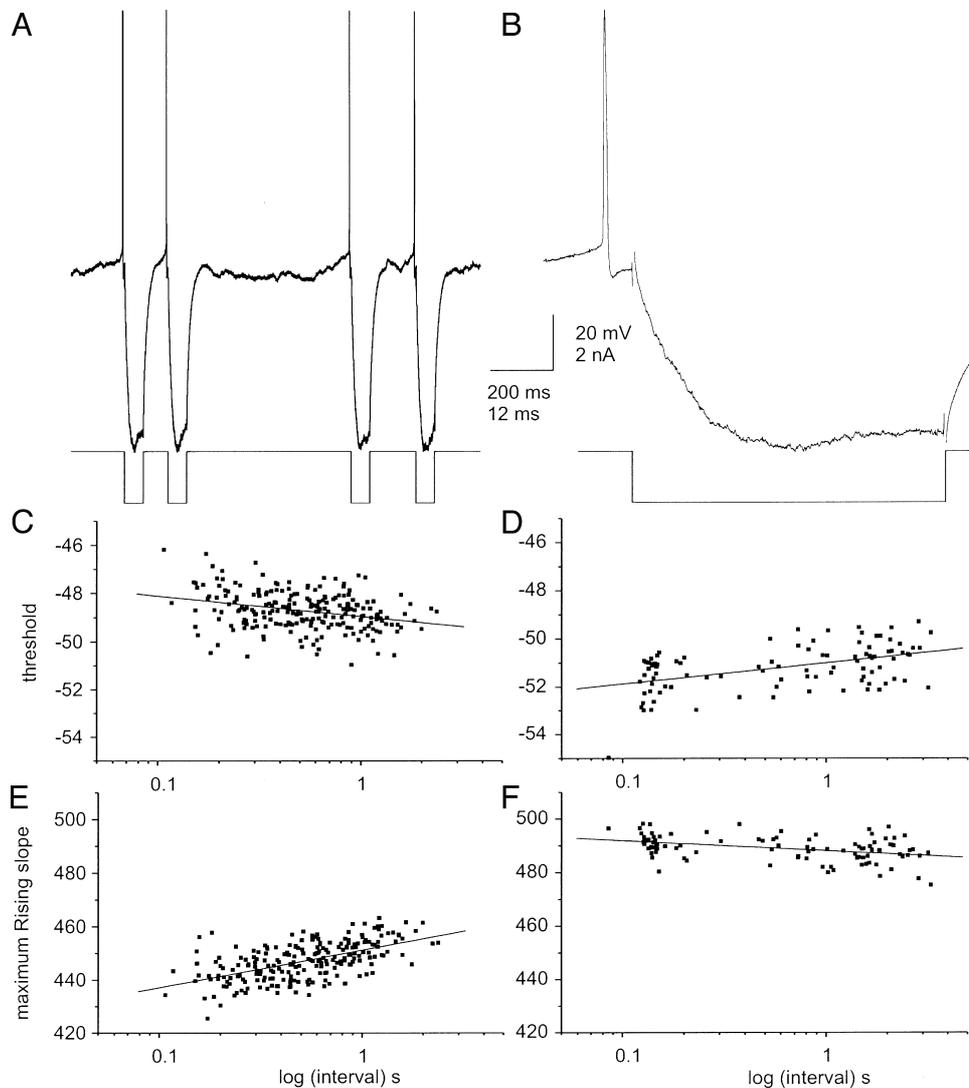


Fig. 6. The effect of previous action potentials on threshold and maximum rising slope is abolished or reversed by intervening strong hyperpolarization. (A) Upper trace: example of action potentials followed by strong hyperpolarizations triggered by the occurrence of the action potentials. Lower trace: the currents injected following the action potential trigger. (B) Expanded view of the first action potential-hyperpolarization complex. In both A and B, the capacitive transients associated with the injected currents have been truncated. (C) Plot of action potential threshold versus log ISI for this cell including best-fit line during control conditions ($R = -0.300$, $P < 0.0001$, $n = 225$ action potentials). (D) Plot of action potential threshold versus log ISI during period where each action potential was followed by a hyperpolarization. Notice that the negative relationship shown in C is reversed during this period ($R = 0.46929$, $P < 0.0001$, $n = 97$ action potentials). There also is a generalized shift in the threshold towards more negative values. (E) Plot of action potential maximum rising slope versus log ISI for this cell including best-fit line during control conditions ($R = 0.56599$, $P < 0.0001$, $n = 225$ action potentials). (F) Plot of action potential maximum rising slope versus log ISI for this cell including best-fit line during a period where each action potential was followed by a hyperpolarization. Notice that the positive relationship shown in E is reversed during this period ($R = -0.40314$, $P < 0.0001$, $n = 97$ action potentials). There also is a generalized shift in the maximum rising slope towards more positive values.

to the recording electrode, then it is possible that the neuron is non-isopotential and the voltage at the initiation site is constant across action potentials. For pyramidal cells (Stuart et al., 1997), the action potential initiation site is believed to be the first node of Ranvier under most conditions. We believe that all the recordings included in this data set were obtained from the soma for the following reasons: (1) all of our recordings exhibited action potentials with peak potentials greater than 0 mV and (2) all of our action potentials had distinct afterhy-

perpolarizations (mean amplitude of 12.2 mV). These properties are distinct characteristics of action potentials recorded from the somatic region (Kamondi et al., 1998).

Argument for a sodium-channel-based mechanism

Previous work has shown that the threshold voltage for action potential initiation can depend on the rate change of the membrane potential (Noble and Stein, 1966; Calvin, 1974; Schlue et al., 1974; Stafstrom et

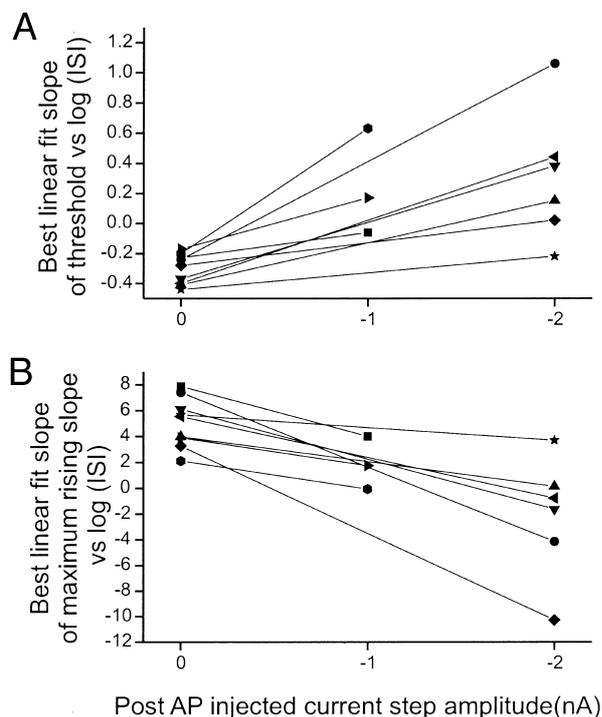


Fig. 7. Summary of the effect of intervening strong hyperpolarization on action potential (AP) threshold and maximum rising slope. (A) Slopes of the linear fits between threshold and log ISI from control and triggered hyperpolarization recording periods for the nine cells where tested. (B) Same as in A but for maximum rising slope and log ISI.

al., 1984; Azouz and Gray, 2000). This sensitivity of the threshold to the rate of membrane change is mediated by the gating kinetics of the sodium and potassium channels (Hodgkin and Huxley, 1952a; Noble, 1966). Slow changes in membrane potential change the relative starting positions of the sodium and potassium channels along their activation and inactivation curves.

The mechanism behind the relationship between threshold of action potentials and the occurrence of previous action potentials within ~ 1 s has not been investigated. Based upon the data presented above, the intrinsic mechanism which mediates the threshold-ISI interaction must meet several criteria. It must be activated by single action potentials, it must have a relatively long decay/recovery time, and its decay/recovery must be accelerated by strong hyperpolarization. While no known potassium channel meets all of the criteria, the voltage-gated sodium channel does. Brief depolarizations result in the inactivation of a fraction of the sodium channels, some of which recover with a slow time constant (Mickus et al., 1999). The slow time constant for sodium channel recovery has been reported to be approximately 1 s (Jung et al., 1997; Colbert et al., 1997; Mickus et al., 1999). In addition, strong hyperpolarization will also accelerate the recovery from inactivation of sodium channels (Spruston et al., 1995; Mickus et al., 1999). In addition, sodium channels predominate the early phases of the action potential including the thresh-

old and the maximum rising slope of the action potential. The findings that the maximum rising slope is also affected by the occurrence of previous action potentials within 1–2 s further supports a sodium channel mechanism.

Functional implications

Variations in action potential threshold will play a critical role in determining the firing pattern of neurons. Threshold level can be altered in a general way either by the presence of neuromodulators (e.g. see Figenschou et al., 1996) or by simple changes in the resting membrane potential. The more depolarized a cell's resting potential, the more depolarized the action potential threshold will be (data not shown). As a result, it is likely that the specific firing pattern of a cell will be a function of the resting potential before and during the synaptic input train due to the effects of resting potential on voltage-gated channels that open and close around the resting potential. The neuronal membrane potential and time since the previous action potential modulate the activation and inactivation states of voltage-gated channels such as the sodium channels. These data suggest that the more hyperpolarized the membrane or the longer the time elapsed since the previous action potential, the more sodium channels will be available for activation. The increased availability of sodium channels will facilitate the induction of subsequent action potentials from smaller depolarizations. This mechanism may be viewed as a cellular form of 'short-term memory' in the tens of milliseconds to 1 s time range. This range is well within the range of the observed firing rates of CA1 pyramidal cells during behavior (1–15 Hz; Hirase et al., 1999).

This short-term 'memory' effect has important implications for the precise patterning of neuronal output for a given pattern of input. Previous work has shown that the response to repeated presentations of a fluctuating stimuli generates a highly reliable spike train output (Mainen and Sejnowski, 1995). This indicates that individual cells reliably transduce their inputs. Other work has demonstrated that excitatory input synchrony is an important factor in determining whether or not an action potential will occur at any given time during a pattern of input (Stevens and Zador, 1998; Azouz and Gray, 1999, 2000). Our work extends upon these works and suggests that the precise timing of action potential initiation is a complex function of both synaptic input properties (e.g. synchrony) and the intrinsic state of the cell as determined by intrinsic conductances such as voltage-gated sodium channels. An example of what this interaction means for neuronal firing patterns can be seen in Fig. 1 of Mainen and Sejnowski (1995). On occasions when an action potential was spontaneously 'dropped or added' then the timing of several subsequent action potentials were also disrupted. Our data predicts that the period of disrupted firing should be determined at least in part by the occurrence of a long enough silent period to allow effects of prior spikes to decay. The data presented here suggests that the specific firing pattern observed in

response to repeated exposures of a fluctuating stimulus could be systematically altered by the systematic induction of action potentials in the period prior to or during the stimulus train. Another example can be seen in Penttonen et al., 1998. There we show that the temporal precision of the spiking response to a large depolarizing step combined with commissural synaptic stimulation can be increased when the synaptic stimulation evokes an initial action potential as compared to when there is no synaptically evoked action potential.

Another implication of these data concerns the effect of the resting membrane potential on the action potential. It is known that the mean subthreshold resting potential modulates the number of sodium channels available for action potential initiation (Hodgkin and Huxley, 1952a,b). This suggests that simple modification of the resting potential may result in different specific patterns of neuronal firing in response to a pattern of

suprathreshold inputs due to alterations in the mean action potential threshold.

Finally, it has been shown that the magnitude of sodium channel inactivation is subject to modulation via neuromodulators such as acetylcholine (Tsubokawa and Ross, 1997) or via intracellular kinases such as protein kinase C (Colbert and Johnston, 1998). These observations combined with the present findings suggest that the relationship between fluctuations in intracellular membrane potential and the occurrence of an action potential is regulated by complex mechanisms including voltage-gated channels which are modulated by the cell's own previous output.

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REFERENCES

- Azouz, R., Gray, C.M., 1999. Cellular mechanisms contributing to response variability of cortical neurons *in vivo*. *J. Neurosci.* 19, 2209–2223.
- Azouz, R., Gray, C.M., 2000. Dynamic spike threshold reveals a mechanism for synaptic coincidence detection in cortical neurons *in vivo*. *Proc. Natl. Acad. Sci. USA* 97, 8110–8115.
- Bryant, H.L., Segundo, J.P., 1976. Spike initiation by transmembrane current: a white-noise analysis. *J. Physiol. (Lond.)* 260, 279–314.
- Buzsáki, G., Leung, L.W., Van derwolf, C.H., 1983. Cellular bases of hippocampal EEG in the behaving rat. *Brain Res.* 287, 139–171.
- Calvin, W.H., 1974. Three modes of repetitive firing and the role of threshold time course between spikes. *Brain Res.* 69, 341–346.
- Colbert, C.M., Johnston, D., 1998. Protein kinase C activation decreases activity-dependent attenuation of dendritic Na⁺ current in hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* 79, 491–495.
- Colbert, C.M., Magee, J.C., Hoffman, D.A., Johnston, D., 1997. Slow recovery from inactivation of Na⁺ channels underlies the activity-dependent attenuation of dendritic action potentials in hippocampal CA1 pyramidal neurons. *J. Neurosci.* 17, 6512–6521.
- Figenschou, A., Hu, G.Y., Storm, J.F., 1996. Cholinergic modulation of the action potential in rat hippocampal neurons. *Eur. J. Neurosci.* 8, 211–219.
- Gutkin, B.S., Ermentrout, G.B., 1998. Dynamics of membrane excitability determine interspike interval variability: a link between spike generation mechanisms and cortical spike train statistics. *Neural Comput.* 10, 1047–1065.
- Henze, D.A., Gonzalez-Burgos, G.R., Urban, N.N., Lewis, D.A., Barrionuevo, G., 2000. Dopamine increases excitability of pyramidal neurons in primate prefrontal cortex. *J. Neurophysiol.* 84, 2799–2809.
- Henze, D.A., Harris, K.D., Buzsáki, G., 1999. Spike patterns influence action potential threshold *in vivo*. *Soc. Neurosci. Abstr.* 25 (1392), 1392.
- Hirase, H., Czurko, A., Csicsvari, J., Buzsáki, G., 1999. Firing rate and θ -phase coding by hippocampal pyramidal neurons during 'space clamping'. *Eur. J. Neurosci.* 11, 4373–4380.
- Hodgkin, A.L., Huxley, A.F., 1952a. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.)* 117, 500–544.
- Hodgkin, A.L., Huxley, A.F., 1952b. The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*. *J. Physiol. (Lond.)* 1952, 497–506.
- Jung, H.Y., Mickus, T., Spruston, N., 1997. Prolonged sodium channel inactivation contributes to dendritic action potential attenuation in hippocampal pyramidal neurons. *J. Neurosci.* 17, 6639–6646.
- Kamondi, A., Acsády, L., Buzsáki, G., 1998. Dendritic spikes are enhanced by cooperative network activity in the intact hippocampus. *J. Neurosci.* 18, 3919–3928.
- Kempter, R., Gerstner, W., van Hemmen, J.L., Wagner, H., 1998. Extracting oscillations. Neuronal coincidence detection with noisy periodic spike input. *Neural Comput.* 10, 1987–2017.
- Magee, J.C., 1998. Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. *J. Neurosci.* 18, 7613–7624.
- Mainen, Z.F., Sejnowski, T.J., 1995. Reliability of spike timing in neocortical neurons. *Science* 268, 1503–1506.
- Mickus, T., Jung, H., Spruston, N., 1999. Properties of slow, cumulative sodium channel inactivation in rat hippocampal CA1 pyramidal neurons. *Biophys. J.* 76, 846–860.
- Noble, D., 1966. Applications of Hodgkin–Huxley equations to excitable tissues. *Physiol. Rev.* 46, 1–50.
- Noble, D., Stein, R.B., 1966. The threshold conditions for initiation of action potentials by excitable cells. *J. Physiol. (Lond.)* 187, 129–162.
- Penttonen, M., Kamondi, A., Acsády, L., Buzsáki, G., 1998. Gamma frequency oscillation in the hippocampus of the rat: intracellular analysis *in vivo*. *Eur. J. Neurosci.* 10, 718–728.
- Schlue, W.R., Richter, D.W., Mauritz, K.H., Nacimiento, A.C., 1974. Responses of cat spinal motoneuron somata and axons to linearly rising currents. *J. Neurophysiol.* 37, 303–309.
- Softky, W.R., Koch, C., 1993. The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. *J. Neurosci.* 13, 334–350.
- Spruston, N., Schiller, Y., Stuart, G., Sakmann, B., 1995. Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. *Science* 268, 297–300.
- Stafstrom, C.E., Schwindt, P.C., Flatman, J.A., Crill, W.E., 1984. Properties of subthreshold response and action potential recorded in layer V neurons from cat sensorimotor cortex *in vitro*. *J. Neurophysiol.* 52, 244–263.
- Stevens, C.F., Zador, A.M., 1998. Input synchrony and the irregular firing of cortical neurons. *Nat. Neurosci.* 1, 210–217.

- Stuart, G., Spruston, N., Sakmann, B., Hausser, M., 1997. Action potential initiation and backpropagation in neurons of the mammalian CNS. *Trends Neurosci.* 20, 125–131.
- Troyer, T.W., Miller, K.D., 1997. Physiological gain leads to high ISI variability in a simple model of a cortical regular spiking cell. *Neural Comput.* 9, 971–983.
- Tsubokawa, H., Ross, W.N., 1997. Muscarinic modulation of spike backpropagation in the apical dendrites of hippocampal CA1 pyramidal neurons. *J. Neurosci.* 17, 5782–5791.
- Wickens, J.R., Wilson, C.J., 1998. Regulation of action-potential firing in spiny neurons of the rat neostriatum *in vivo*. *J. Neurophysiol.* 79, 2358–2364.

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