A THEORETICAL COMPUTER MODEL OF CELLULAR MODIFICATION ASSOCIATED WITH OLFACTORY LEARNING IN THE RAT PIRIFORM CORTEX

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Abstract

Learning associated cellular modifications were previously studied experimentally in the rat piriform cortex after operand conditioning. The action potential AHP in trained rats was reduced (19 %) and spike trains showed decreased adaptation during long depolarization. However, this reduced AHP amplitude in 'trained' rats depresses EPSP amplitude more effectively than in "pseudotrained" and "naive" rats (control groups). The aim of the computer model was to explain this paradox of increased EPSP depression after learning. Three models were used to simulate the exact reduction in the AHP amplitude: 1. *"Conductance change"* – decreasing g_{kCa} by 40 %. 2.*"Moving"*- shifting the location of the dendritic segment that exhibits active conductances (including AHP conductance) distally from the soma, accompanied by g_{kCa} decrease of only 15 %. "*Shrinkage*"- decreasing the length of the AHP dendritic segment, accompanied by an increase of g_{kCa} by 9 %. Moving the synaptic input distally from the soma enhanced EPSP depression by the AHP conductance. Hence, the learning process could be simulated by a "jump" from the control curve to any curve representing decreased AHP amplitude. Yet the enhanced EPSP depression required additional shift of the EPSP input to more distal locations.

Introduction

Cellular modifications associated with olfactory learning in the rat piriform cortex following operand conditioning have been studied previously in our laboratory [1-5]. "Trained" rats were trained in a 4-arm maze to discriminate positive cues in pairs of odors. Training continued until rats acquired the rule of learning, usually after learning the first or second pair of odors. "Pseudotrained" and "naive" rats served as controls. "Pseudotrained" rats were reward randomly thus they were unable to learn and the "naive" rats were never exposed to the experimental protocol. The training reduced the action

potential AHP in the pyramidal cells and decreased their adaptation during firing induced by a depolarizing step only in trained rats. Later study indicated that learning reduced mainly the slow I_{AHP}, a Ca^{2+}-dependent potassium current that dominates AHP amplitude (Bosh and Barkai, unpublished). EPSPs evoked by neighboring pyramidal cells were increased after training. Yet, interestingly, inhibition of these EPSPs during maximal AHP conductance (following a short train of action potentials) was more effective after learning [3].

The aim of the present computer study was first to simulate the results and than to explain how in the trained rats inhibition of EPSP during maximal AHP conductance is more effective despite the reduction in its amplitude. Alternatives models such as changes in size, location and maximal potassium conductance of the AHP were explored. It is suggested that a change in the distance between the EPSP's input site and the proximally AHP conductance location [6] could be a possible explanation for this paradoxical phenomena.

Method

The modeling of the piriform pyramidal neuron was executed by a NEURON simulator [7]. The cell was composed of a soma and a single unbranched dendrite. The length and width of the dendrite were 1300 μm and 2 μm, respectively, and these of the soma were 10 μm and 10/π μm, respectively. The dendrite was reconstructed by 26, 50 μm long, isopotential compartments. The passive parameters were: uniformly distributed membrane resistance (R_m) of 30000 Ω/cm^2 and capacitance (C_m) of 1 μF/cm^2. Cytoplasmic resistance (R_i) was 100 Ωcm. At the soma the voltage dependent channels were sodium conductance (g_{Na}) of 8571 pS/μm^2 and delayed rectifier potassium conductance (g_{DR}) of 628 pS/μm^2. At the dendrites, g_{Na} was 2.3 pS/μm^2 and the potassium conductances contain M current conductance (g_m) of 0.014 pS/μm^2, g_{DR} of 5 pS/μm^2 and calcium dependent potassium conductance (g_{kCa}) of 2000 pS/μm^2 while the calcium conductance was (g_{Ca}) 0.06 pS/μm^2. The voltage-dependent and AHP generating conductances were located only in a 300 μm long proximal dendritic segment. The reversal potentials of the sodium, potassium and calcium currents were 50 mV, -90 mV and 140 mV, respectively. EPSP conductance was simulated by an α-function with a maximal conductance of 1 nS. The time to maximal conductance (τ) was 0.5 ms. The reversal potential of the EPSP was 0 mV.

As in the above mentioned experiments, a standard AHP was induced by six action potentials initiated during a somatic current injection of 100 ms. AHP amplitude was measured relative to the resting potential of -80 mV. In all the simulations EPSP was introduced at the time of maximal AHP amplitude (50 ms after the termination of the 6th spike), and its depression was compared to the control values. EPSP amplitude was always measured at the soma.

Results

Simulation of the reduction of AHP amplitude

Under experimental conditions, the AHP – related EPSP reduction in the "trained" rats was 16.5 %, whereas at the "naive" and "pseudotrained" rat it was reduced only by 12.1 % [2]. Paradoxically the more effective inhibition of the EPSP in the "trained" rats was associated with a 19 % decrease of AHP amplitude. Such a reduction was not observed in the control groups. However, the magnitude of g_{AHP} yielding such an AHP amplitude depression is not known. Three distinct alterations of the control parameters could provide a similar decrease of the AHP amplitude: 1. *"Conductance change"*- decreasing g_{kCa} by 40 % compared to the control without any other changes. 2.*"Moving"*- moving the location of the active conductance area distally from the soma, with no alteration of its length. But, in order to reduce the AHP amplitude by 19%, the g_{kCa} had to be reduced in addition by only 15 %. 3. "*Shrinkage*"- decreasing the length of the active conductance dendritic area from 300 μm to 100 μm adjusted by a small increase of g_{kCa} by 9 %. The simulated action potentials and the resultant AHP were similar to the experimental results (fig 1).

EPSP reduction due to the AHP conductance (g_{AHP})

After obtaining reduction of 19 % of AHP amplitude in each of the three models, the resting potential was set to the potassium's reversal potential (-90 mV, without any additional changes) in order to simulate the shunt effects of the g_{AHP} on the EPSP. An EPSP was initiated at the AHP maximal conductance, 50 ms after the 6^{th} spike. The isolated affected EPSP was obtained after subtracting the trace of the 6 spike alone from the trace of the 6 spike plus the EPSP. This isolated EPSP was compared to the normal single EPSP (fig 1) for evaluating the percent of inhibition (%inhibition=100(EPSP-isolated EPSP)/EPSP) . We further systematically examined in the three models the effect of moving the EPSP input away (distal) from the soma. Somatic measured EPSPs became smaller with distance as may be expected for a passive spread. However, surprisingly, the EPSP depression by the g_{AHP} was relatively more effective. The relation between the EPSP reduction and its site of initiation exhibited a sigmoidal function (fig 2). In order to understand the cause of this depression, the EPSP was measured also at two other sites. First, EPSPs were measured at the input site in the presence of g_{AHP}. At all locations a similar response with no decline was obtained (see filled triangles curve at fig 2). Second, the EPSPs from each synaptic location were measured at a compartment just distal to the active dendritic area (300 μm distal to the soma).

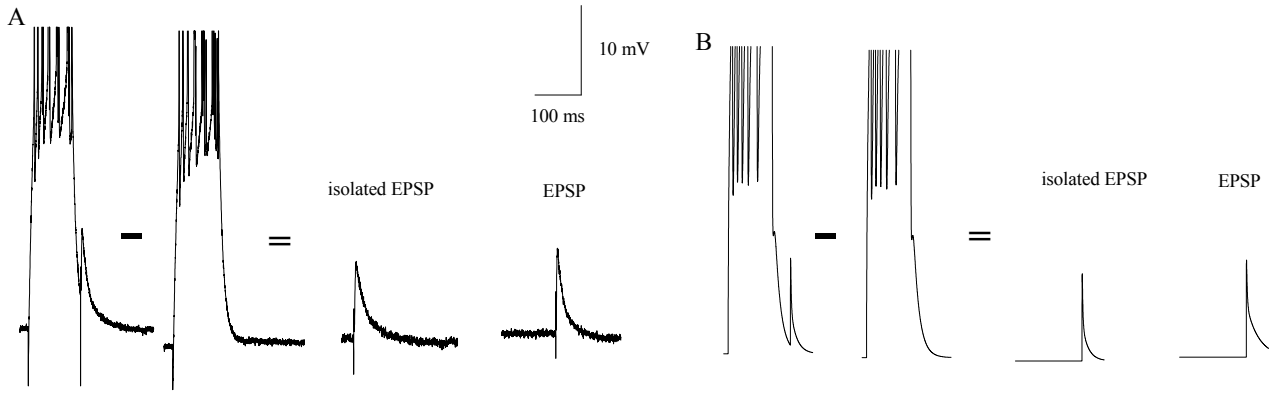

Fig 1. Depression of EPSP during the maximal AHP conductance. EPSP was initiated 50 ms after the termination of the 6th spike. The resting potential was determined at –90 mV, the potassium reversal potential, in order to avoid hyperpolarization. An isolated EPSP was obtained, experimentally (A, Saar, Grossman and Barkai, unpublished) and theoretically (B), after subtracting the response of the six spikes from the response including these spikes and the EPSP. Subsequently this isolated EPSP was compared with the control EPSP in order to determine its reduction.

The difference between this measured EPSP inhibition relative to the inhibition obtained at the soma was 10-15% (fig 2; compare filled rectangles curve with filled circles curve). So, the contribution of the active dendritic segment to the depression of the EPSP is constant and independent of the synaptic input location. But, increasing the distance between the active segment and the EPSP input location by additional passive segments, significantly improved the EPSP depression by the g_{AHP}.

The above-mentioned paradoxical phenomenon of increased EPSP depression despite diminished AHP amplitude could be explained by a "jump" from the control curve to one of the other curves representing 19% decreased AHP amplitude. This "jump" obviously involves movement of EPSP input to more distal point from the soma. According to the models the process of learning could be as follows: under control conditions, AHP reduced EPSP amplitude by 12.1 %. This fits a possible position of the EPSP input on the dendrite 420 μm (y=12.1, x=2.4; 2.4·50+300) distally from the soma (fig 2). In order to simulate the 16.5% decrease of EPSP by the AHP after training while the AHP amplitude is reduced by 19 %, the synaptic input has to 'move' to either of the possible locations on the dendrite:

Model 1: 690 μm (y=16.5, x= 8.8; (8.8-1)· 50+300 = 690) .

Model 2: 710 μm (y=16.5, x= 9.2; (9.2-1)· 50+300 = 710).

Model 3: 555 μm (y=16.5, x= 6.1; (6.1-1)· 50+300 = 555).

The predicted EPSP location shift in models 1, 2 and 3 are 270, 290 and 135 μm, respectively. Thus, the common prediction for all the models is that the training associated changes may result from a shift to distal location of the synaptic inputs.

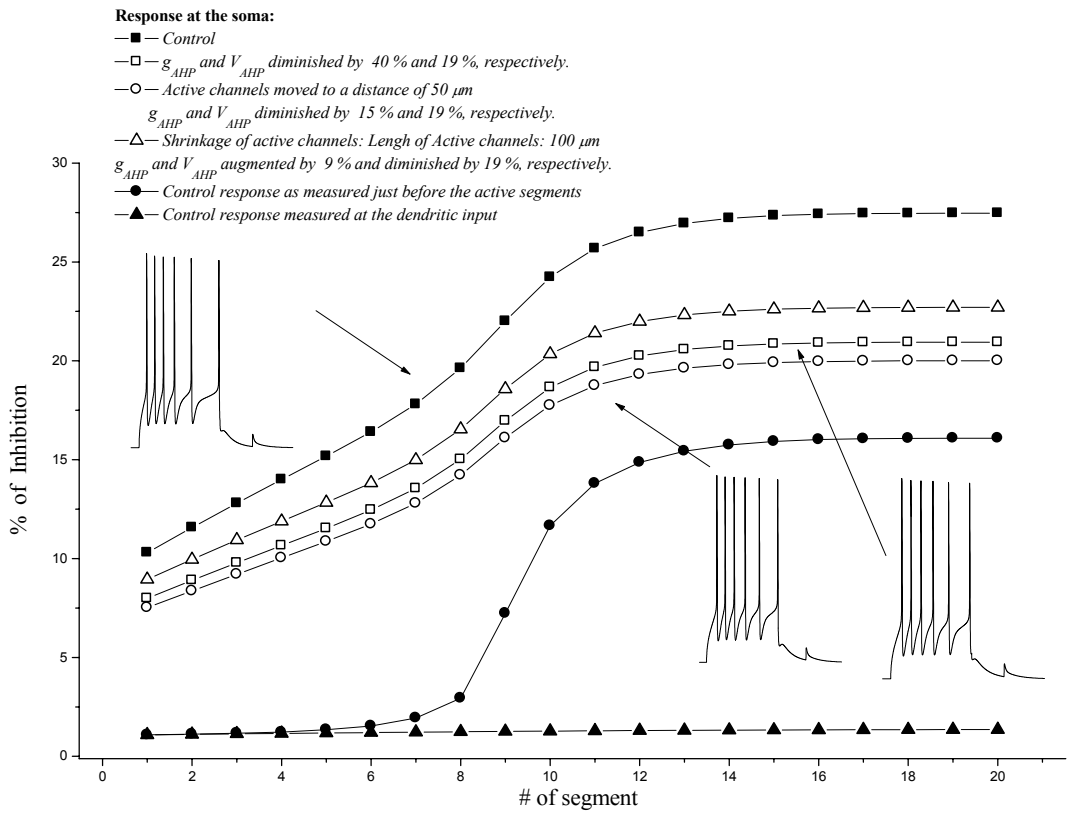

Fig 2. A cellular model of learning that explains the observation of enhanced EPSP inhibition by decreased AHP amplitude. The x-axis is the 1000 μm long passive dendrite, divided to segments, each one with a length of 50 μm. In the control condition the soma is separated from this passive dendrite by a 300 μm long dendrite containing active conductances. Segment "1" means the first passive segment next to the active dendrite. A 19 % decrease of the AHP amplitude, as a result of learning, could be simulated by three models: decrease of g_{KCa} by 40 % (□, with no additional changes), reduction of the g_{KCa} by 15 % and a distally movement of the active dendrite (○) and a shrinkage of the active dendrite and an enhancement of g_{Kca} (Δ). According to the experiments, after learning g_{AHP} reduced EPSP by 16.1 %. At all three models in order to enhance this inhibition after learning, the synaptic input locations had to move distally (135- 290 μm, see the text) from the soma. To simulate g_{AHP} decrease, in parallel a "jump" from the control condition (■) to either one of the curves has to occur. The EPSP inhibition measured at the location of the synaptic input (▲) is equal along the dendrite. The difference between the EPSP inhibition recorded at the soma in the control condition (■) and the inhibition measured just before the active dendrite (●) in the same state is more or less constant, independent of the synaptic input location. This means that the length of the passive dendrite is the main cause for the distinct EPSP inhibition by the g_{AHP}.

Conclusions and discussion

The main prediction of the present simulation is that learning related changes in AHP and EPSP depression could be associated with a combination of reduction in the effective shunt of the AHP and a relative shift of the synaptic input distally from the soma. Whereas we can not prefer one mechanism or another to reduce the AHP, model 1 would be the simplest one since it involves only a single

parameter change (g_{KCa}). Yet, the expected change should be large (40%). Models 2 and 3 involve additional parameter of shortening or shift of the AHP active membrane location, but the required shift in the synaptic input location in model 3 is smaller than in model 1. It is worth noticing that the olfactory learning process has been shown to involve long-term changes in spine density in the piriform pyramidal cells [8]. This indicates that changes in synaptic input may occur and thus change of synaptic 'center of impact' may also shift.

The use of g_{KCa} to simulate modulation of AHP amplitude seams reasonable since experimental evidence [9] corroborated by BAPTA injection to the same cells [10] suggest this conductance is at least partially involved with the physiological observed changes.

An interesting finding of our simulation is that the distance between the synaptic input and the g_{AHP} segment, representing a passive dendrite segment, is crucial in determining the amount of EPSP depression recorded in the soma [11]. Similar results were reported by us using simulation of α-motoneurons [12]. In this system the proximally located inputs of reciprocal inhibition depress distally distributed Ia-EPSP more efficiently than recurrent inhibition whose synaptic inputs are co- localized with the excitatory inputs.

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