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Modeling stress-induced adaptations in Ca^{2+} dynamics

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Abstract

A hippocampal stress response is mediated by the glucocorticoid and mineralocorticoid receptors and involves primarily delayed changes in hippocampal neuronal properties. In this study, we concentrate on stress-induced effects in CA1 neurons which include an enhancement of the slow afterhypolarization (sAHP), an increase in Ca^{2+} currents, specifically a presumed upregulation of the $Ca_v1.2$ subunit that mediates one type of the *L*-type Ca^{2+} currents (the Ls type), and a suppression of Ca^{2+} extrusion mechanism, manifested as a decrease in plasma membrane Ca^{2+}-ATPase-1. The aim of our study lies in identifying a causal relationship between either or both of the changes in the Ca^{2+} dynamics system and the increase in the sAHP. We used a compartmental CA1 pyramidal neuron model that included detailed structural properties and biophysical mechanisms and was implemented in the NEURON simulation environment. The model incorporated equations for 16 types of ionic mechanisms, known to be present in CA1 pyramidal cells. Among these, both types of *L*-type Ca^{2+} current, one with normal activation kinetics (Ls) and one with additional prolonged openings (Lp), Ca^{2+}-activated K^+ conductances that underlie the AHP (I_{sAHP}), and an integrated modeling equation for intracellular Ca^{2+} decay comprising all Ca^{2+} extrusion and buffering mechanisms were included. We found that the enhancement of sAHP could be explained partially not by an increase in Ls Ca^{2+} current, but rather by a decrease in the rate of intracellular Ca^{2+} decay. Furthermore, we suggest that an additional 50% increase in the I_{sAHP}, along with the change in the Ca^{2+} extrusion mechanism, could fully explain the experimental findings. Previous modeling work from our lab suggested that there might be a causal effect between an increase in the Lp Ca^{2+} current and the aging-induced enhancement of the sAHP. However, a respective causal relationship between an increase in the Ls Ca^{2+} current and sAHP enhancement does not seem to exist, probably due to their differential contribution to intracellular Ca^{2+} levels. Experimental and computational evidence imply that aging and stress may induce different Ca^{2+}-dependent cellular adaptations in CA1 neurons, which however, result in a similar phenotype of enhanced sAHP and subsequent decreased neuronal excitability.

Keywords: Hippocampus; Slow afterhyperpolarization; NEURON

1. Introduction

Stressful stimuli evoke a generalized stress response in an organism as an attempt to initiate homeostatic mechanisms as well as to enable adaptation. The stress response involves, among other effects, the secretion of the corticosterone hormone from the adrenal glands, which acts on brain glucocorticoid (GR) and mineralocorticoid receptors (MR) to signal the presence of stressful stimuli [6]. The hippocampus expresses both types of receptors at high levels [17], therefore, an increase in corticosterone levels could impact on the properties of hippocampal neurons including Ca^{2+} currents [28]. Acute elevation of corticosterone levels induce both immediate and delayed changes in hippocampal Ca^{2+} currents [7].

The immediate effects of corticosteroids-like cortisol include a decrease in high-voltage activated (HVA) Ca^{2+} currents (both *L* and *N*-type) [13] without an effect on spontaneous firing or the passive membrane properties of CA1 pyramidal neurons [1,16,22]. However, the delayed response to the enhancement of corticosterone levels includes various adaptations of the electrical properties of CA1 pyramidal neurons. Peripheral administration of

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corticosterone results in decreased firing of hippocampal neurons [29], which could be explained by an increase in the sAHP [16,22]. The sAHP is mostly mediated by Ca^{2+}-activated K^+ current, carried by SK channels [4]. Thus, alterations in intracellular Ca^{2+} dynamics could modify the function of those channels and subsequently the I_{sAHP}. Consistent with this view is the observation that Ca^{2+} potentials [22] and Ca^{2+} currents, most likely the *L*-type Ca^{2+} current, [20,23] are increased in hippocampal CA1 neurons 60–90 min following corticosterone administration. Recent evidence suggests a selective upregulation of the $Ca_v1.2$ subunit—in rat but not mouse hippocampal cells (P.Chameau et al., unpublished observation) and in rat basolateral amygdala cells [19], which would result in a 2-fold increase of the Ls Ca^{2+} current (P.Chameau et al., unpublished observations). The $Ca_v1.2$ subunit produces an *L*-type Ca^{2+} current (referred to as Ls Ca^{2+} current) with faster activation kinetics compared to the current mediated by the $Ca_v1.3$ subunit (referred to as Lp Ca^{2+} current) [25]. The effects of stress on the Ca^{2+} currents and the sAHP are similar to the changes observed in the hippocampus of aged animals [21,24], suggesting the existence of common mechanisms involved in both conditions.

Corticosterone administration increases both basal and stimulated intracellular Ca^{2+} levels. Although this elevation could partly be explained by an increase in Ca^{2+} entry through the upregulation of voltage-gated Ca^{2+} channels, changes in the Ca^{2+} extrusion mechanism are also thought to contribute [9,10]. In support of this hypothesis, corticosterone was found to decrease the mRNA levels of a gene coding for plasma membrane Ca^{2+}-ATPase-1 (PMCA-1) [3], which is shown to be necessary for maintaining the levels of intracellular Ca^{2+} [2]. This downregulation may account for the approximately 40% decrease in the rate of Ca^{2+} removal from the cytoplasm [18].

Although all of the above stress-induced adaptations have been observed in CA1 pyramidal neurons of the hippocampus, experimental difficulties prevent the study of causality among these different changes. For this reason, we utilized computational tools to determine whether the stress-induced enhancement of *L*-type Ca^{2+} currents and/or the decrease in the function of Ca^{2+} extrusion mechanisms can account for the increased sAHP and spike frequency adaptation observed in these neurons.

2. Methods

The compartmental model of a CA1 pyramidal neuron was implemented in the NEURON simulation environment [15]. The biophysical model, the morphology of which is shown in Fig. 2 (centre), is a refinement of a previous model described in [12]. The model consists of 183 compartments and includes a variety of passive and active membrane mechanisms known to be present in CA1 pyramidal cells. We assume a uniform membrane resistance $Rm = 40\,k\Omega\,cm^2$; a uniform intracellular resistivity $Ra = 70\,\Omega\,cm$; and a specific membrane capacitance of $1.0\,\mu F\,cm^{-2}$. The resting membrane potential of the model neuron is -66 mV. Active mechanisms include two types of Hodgkin–Huxley-type Na^+ currents (axonal: I_{na}^a; dendritic: I_{na}^d), three voltage-dependent K^+ currents (I_{Kdr}; I_A; I_M), a fast Ca^{2+} and voltage-dependent K^+ current, I_{fAHP}; a slow Ca^{2+}-dependent K^+ current, I_{sAHP}; a hyperpolarization-activated non-specific cation current (I_h), a low-voltage activated calcium current I_{caT}; three types of Ca^{2+}- and voltage-dependent calcium currents, I_{caN}; I_{caR} and I_{caL}; and a persistent sodium current I_{Nap}. Channel equations, distributions and densities of I_{na}, I_{Kdr} and I_A are described in [26,30]. One difference with the previous model is the use of two different *L*-type Ca^{2+} mechanisms, the Ls and Lp Ca^{2+} currents, with the latter having a delayed-activation component [23].

3. Results

Experimental data have shown that treatment of CA1 neurons in brain slices with glucocorticoid agonists doubles the amplitude and increases the decay kinetics of the sAHP (Fig. 1(a)). The sAHP was simulated in the CA1 neuron model using the same stimulation protocol as in the experiments (Fig. 1(b), left column). Experimentally, two different changes have been observed in Ca^{2+}-dependent mechanisms that could account for the sAHP increase: (1) a doubling in the *L*-type, and most likely the Ls, current and (2) a 40% decrease in the rate of Ca^{2+} extrusion after GR agonist treatment [18]. Therefore, these changes were applied in the CA1 neuron model to determine their effect on the sAHP. First, the Ls current conductance was doubled. However, this caused no difference in the amplitude or kinetics of the sAHP (Fig. 1(c)), suggesting that the stress-induced adaptation on the Ls Ca^{2+} current does not funnel into modulating the sAHP. Second, the time constant of decay for the Ca^{2+} extrusion mechanism was increased by 40%, thus decreasing the rate of Ca^{2+} removal and prolonging the increase in intracellular Ca^{2+} concentration (Fig. 1(d), right column). Under these conditions, the amplitude of the sAHP increased by 45% from 2.2 to 3.2 mV, and its duration was significantly prolonged (Fig. 1(d), left column). However, experimentally, the sAHP amplitude is doubled [16], suggesting that additional mechanisms, possibly at the level of the ionic channels that mediate the sAHP, are induced under conditions of stress. Increasing the I_{sAHP} by 50% in the model cell resulted in an increase of the sAHP by 1 mV (Fig. 1(e)). When the time constant of decay for Ca^{2+} extrusion, the Ca^{2+} Ls current and the I_{sAHP} were changed as mentioned above, the simulated sAHP was doubled compared to the control sAHP and its duration increased, resembling the sAHP change seen in brain slices following GR agonist treatment (Fig. 1(b), right column). This new "cell" simulating the CA1 neuron under GR agonist treatment will be referred from now on as the