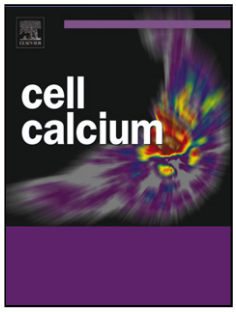

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Where have all the Orais gone? Commentary on "Orai1 Channels Are Essential for Amplification of Glutamate-Evoked Ca^{2+} Signals in Dendritic Spines to Regulate Working and Associative Memory"

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Highlights

- Orai1 was suggested to amplify dendritic spine Ca^{2+} signals
- However, Orai2 more abundant than Orai1 in dendritic spines of hippocampal neurons
- Roles of Orai2 and Orai3 in hippocampal neurons were not addressed
- The contribution of IP_3-dependent Ca^{2+} release was not considered

Abstract

Orai1 channels were reported as critical contributors to the Ca^{2+} signal in hippocampal neurons underlying synaptic plasticity associated with learning and memory. We discuss the results in view of conflicting other reports that stressed the roles of Orai2 channels but failed to detect functions of Orai1 channels in these neurons.

Ca^{2+} ions play a decisive role for long-term potentiation (LTP), the best established cellular mechanism for learning and memory [1]. Not only that Ca^{2+} ions are needed for the release of the neurotransmitter glutamate from presynaptic terminals, but there is also an absolute requirement for Ca^{2+} entry through N-Methyl-D-aspartate (NMDA) receptor channels in

postsynaptic dendritic spines. A block of the NMDA receptor-dependent Ca^{2+} entry prevents the induction of LTP [1]. A recent paper by Maneshi et al. [2] reports a surprising and provocative new twist in the mechanism of the postsynaptic Ca^{2+} signal that triggers LTP. The authors used advanced technologies to show that store-operated Ca^{2+} entry (SOCE), best known for Ca^{2+} signaling in non-neuronal cells [3], might play an outstanding role in the amplification of NMDA receptor-dependent postsynaptic Ca^{2+} accumulations. They conclude that Orai1 channels, mediating SOCE, are 'essential regulators of dendritic spine Ca^{2+} signaling, synaptic plasticity, and cognition'.

The results of Maneshi et al. [2] are particularly interesting because of their description of an unexpected new role of SOCE in neurons. The pioneering work of Hoth and Penner [4] had uncovered SOCE-related Ca^{2+} release-activated Ca^{2+} (CRAC) currents first in mast cells. After years of intense investigations on the molecular basis of CRAC channels, Orai1 proteins were identified as the pore-forming subunits [3]. Simultaneously with Orai1, its two homologues Orai2 and Orai3 were also identified [5]. Orai Ca^{2+} channels reside in the plasma membrane (PM) at endoplasmic reticulum (ER)-PM junctions where they interact with Ca^{2+}-sensing stromal interaction molecules, STIM1 and/or STIM2, that are located in the membrane of the ER [3]. The mechanism of Orai-STIM-mediated SOCE was initially described in immune cells and refined in further studies [3].

SOCE in central mammalian neurons is less well studied. The expression of Orai1 and STIM1 in the brain and their role in store depletion in cultured neurons was first reported in 2009 [6].The results suggested that the molecular mechanism of SOCE in neurons is in many ways similar to that described in non-excitable cells. Specific roles for neurons were reported in later studies. For example, STIM1-dependent SOCE was shown to be important in cerebellar Purkinje neurons for dendritic Ca^{2+} signaling and synaptic transmission involving metabotropic glutamate receptors (mGluRs) [7]. In contrast to non-excitable cells, however, neurons employ additional effective Ca^{2+} signaling mechanisms for ER calcium store homeostasis, foremost voltage-gated Ca^{2+} channels that are routinely activated during action potential activity [7, 8].

Maneshi et al. [2] suggest a direct involvement of Orai1 in activity-dependent synaptic plasticity underlying LTP induction. Their work aims at comprehensively describing the effects of the *Orai1* gene deletion on many levels, ranging from subcellular compartments to animal behavior. The experimental approaches used are cutting-edge.

Especially the variety of different genetic reporters for the detection of Ca^{2+} signals in submembrane nanodomains, vesicle fusion and enzyme activity are remarkable. They propose a rapid mechanism of SOCE activation and deactivation that might be similar to that observed in skeletal muscle. In their model, they speculate that dendritic spine Orai1 channels are activated following a rapid ryanodine receptor-mediated depletion of ER Ca^{2+} stores in response to NMDA receptor-dependent Ca^{2+} entry (Fig. 1), perhaps involving STIM1 and/or STIM2.

While most of their results are in line with a potential role of SOCE in LTP, some of the claims contradict findings reported by other investigators. Unfortunately, highly relevant earlier work is not cited and discussed in the paper. The most serious issue relates to the contributions and roles of the different Orai subunits in CA1 hippocampal pyramidal cells. Maneshi et al. [2] base their study on a presumed 'high' expression of Orai1 in hippocampal neurons. However, the paper that they cite to support this claim expletively says that the expression of Orai1 in the mouse hippocampus is 'low' [9]. In fact, results obtained both from hippocampal tissue and single CA1 pyramidal neurons demonstrate that Orai2 is clearly more abundant than Orai1, with some contribution of Orai3 [10]. Results presented in the Allen Brain Atlas indicate that Orai1 expression is below the detection threshold of *in situ* hybridization [11]. It seems that Maneshi et al. [2] were fooled by an error in the Allen Brain Atlas, as the image that they show in Fig. S1G of their paper does not indicate Orai1 expression, as claimed, but shows the expression of the unrelated protein Tmem132a. The most striking inconsistency comes from a study [12] showing that Orai2, but not Orai1, forms a complex with TRPC6 that underlies STIM2-activated SOCE in similar hippocampal neurons. While an Orai2 deletion caused a drastic reduction in spine SOCE, knock-down of Orai1 had no detectable effect. This is in complete contradiction to the results and conclusions of Maneshi et al. [2] who assigned all effects to Orai1 but did not consider Orai2 at all.

The reasons for the disagreements could be manifold and include the use of different preparations, hidden up- or down-regulation of Orai2 and/or Orai3, and/or a disregarded contribution of mGluR-activation associated with inositoltrisphosphate receptor (IP_3R)-dependent Ca^{2+} release ([13], Fig. 1). Thus, the initial excitement from the first glance on the paper [2] turned into a state of confusion on the role of Orais in hippocampal synaptic plasticity. Obviously, much more work is needed to sort out these contradictory results on Orai functions in central neurons.

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Figure legend

Figure 1. Dendritic spine Ca^{2+} signaling at glutamatergic synapses of hippocampal neurons.

Schematic illustration of the main potential sources for postsynaptic Ca^{2+} signaling at glutamatergic synapses located at dendritic spines of CA1 hippocampal neurons consisting of NMDAR channels, presumably Orai channels, mGluR1/5 and VGCCs. The question marks (in red circles) indicate candidate Ca^{2+} signaling pathways for the induction of LTP that are still under debate.

PM – plasma membrane, ER – endoplasmic reticulum, NMDAR – N-Methyl-D-aspartate receptor, STIM1/2 – stromal interaction molecule1/2, mGluR1/5 – metabotropic glutamate receptor1/5, IP_3R – inositoltrisphosphate receptor, SERCA – sarcoendoplasmic reticulum Ca^{2+} ATPase