Formation of distinct cell populations in the lateral amygdala after auditory fear conditioning – a computational model

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Acquisition of auditory conditioned fear memories requires plasticity at auditory inputs to the dorsal part of the lateral amygdala (LAd). Unit recordings have revealed the presence of two different cell populations in the dorsal (LAdd) and ventral (LAdv) parts of LAd (Repa et al. 2001). During the conditioning phase, several LAdd cells have tone responses that increase and then decrease back to habituation levels (termed transient plastic, TP, cells) whereas the tone responses of a population of LAdv cells gradually increase during conditioning and persist through the extinction phase (termed long-term plastic, LP, cells). We used a conductance-based computational model to investigate how TP and LP cells might be formed after fear conditioning. The model incorporated differential intrinsic connectivity (Samson and Pare, 2006) and distribution of thalamic and cortical afferents, and included the effects of neuromodulation. It was reported recently that LA cells showing activated CREB (cAMP-response element binding protein) were preferentially recruited into the fear memory trace after auditory fear conditioning (Han et al., 2007). CREB modulates the intrinsic excitability of amygdala principal cells by inhibiting sAHP, and increasing their firing frequency (Viosca et al., 2009; Benito and Barco, 2010), without affecting resting membrane potential, input resistance, spike amplitude or the spike half-width (Zhou et al. 2009). The distribution of principal cell types in the model conformed to previous experimental reports (Faber et al., 2001) where principal LA cells were reported to exhibit a continuum of spike frequency adaptation. Accordingly, we modeled three types of principal cells that exhibited rapid (Type A, 60%), intermediate (Type B, 20%) or slow spike frequency adaptation (Type C, 10%). Principal cell types B and C were assumed to be the ones that show activated CREB. We investigated whether the model fear memory trace (LP cells) recruited only cells of types B and C. Sorting the population of model LP cells according to their types, revealed that of the 40 LP cells, 24 were of type B, 16 were of type C, and none were of type A. We then lesioned the LP cells, repeated the protocol, and found that a new set of LP cells replaced the lesioned ones and that, again, they were either of types B or C, supporting the idea that formation of the fear memory trace involves a competitive process between principal cells of type B and C.

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The hippocampus has been suggested as playing a significant role for the persistence of fear memories in studies involving extinction of classically conditioned fear associations in rats. The hippocampus is linked to processing contextual information during fear conditioning and extinction. This process likely involves both place awareness and episodic memory. We developed a biologically realistic network model of the hippocampus by modeling entorhinal cortex, CA3, and dentate gyrus cells of the hippocampus. Three-compartment biologically realistic cell models were developed for each of the regions and tuned to reproduce passive properties and membrane potential responses for current injections. A network model was developed that included a scaled version of the biological cell numbers in those regions. The model was used to study the role of the hippocampus in fear conditioning and extinction, as well as the effects of acetylcholine and dopamine on the network behavior.

It is known that hippocampus can perform pattern separation and completion efficiently. Computational models have suggested how the hippocampus might be implementing this, but such models have tended to be based on artificial neural network cell models. We report a biologically realistic network that used conductance based cell models to reproduce pattern separation and completion, providing insights at a finer biological level. Moreover, our group used simplified Izhikevich models and proposed that pattern separation required higher concentration levels of the neuromodulator acetylcholine (ACH), while lower levels of ACH favored pattern completion (Hummos et al., 2011). This hypothesis was also tested using the biologically realistic model. The model is then used to suggest how hippocampus might help disambiguate between fear and extinction contexts via projections to the prelimbic cortex and to the basal amygdala.

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Distinct tone responsive cell populations in the basal amygdala after fear training

– A modeling study

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A recent study (Amano et al., 2011) suggested functionally redundant contributions of basomedial nucleus (BM) and basolateral nucleus (BL) of the basal amygdala (BA) to the expression of conditioned fear. That study identified three classes of BA neurons on the basis of their responsiveness to auditory conditioned stimuli (CS) during fear conditioning and extinction (also see Herry et al., 2008): (1) Fear cells which increased their responsiveness to the CS through conditioning, but were either unresponsive or inhibited by the end of extinction training, (2) Extinction-resistant cells which were similar to fear cells except that they continued to be responsive to the CS through extinction, and (3) Extinction cells which were initially unresponsive, developed inhibitory responses by early extinction, and these were transformed to excitation by late extinction. Although the proportions of CS-responsive neurons were similar in both nuclei, the CS responses of BM neurons persisted after tone offset. To investigate the network mechanisms that support these contrasting patterns of CS responsiveness, we developed a 3-D biologically realistic network model of the rodent BA. The initial model had multi-compartment Hodgkin-Huxley type single cells and specific connectivity patterns between these cell types. Hebbian plasticity was included in the excitatory AMPA and inhibitory GABA_A receptor-mediated synapses to model learning, using a calcium learning rule. The model had random connectivity among principal cells; interneurons provided inhibition locally; and we implemented hypothetical circuit models suggested in Pare and Duvarci (2012) that involved fear and extinction cells. We first considered the case where the inputs to BA originated solely from LA. For this case, the model showed that cells that received inputs from fear-like LA cells became BA fear cells, and those that received input from extinction-resistant LA cells became BA extinction resistant cells. Interestingly, the hypothetical circuit proposed did result in individual cell behaviors observed in Pare and Duvarci (2012). We are now investigating what roles the additional inputs from the ventral hippocampus (representing context) and the prelimbic cortex might play in either the formation of the BA cell types or in modulating their tone responses.

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Biologically realistic multi-compartmental models of single neurons typically have compartments ranging in number from 1 to over 500. Development of detailed models for single cells is complicated by the fact that not much is known about the computations performed by the dendrites. However, models are being developed for illustrating specific functions such as impact of location of channels and their densities on neuronal response. In parallel, biological data are constantly emerging about how synapses may be integrating the diversity of inputs they receive.

Neuronal network models typically use simplified single cells models with either one or two compartments presently. This is largely due to the fact that computational times become prohibitive if detailed cells models are used. Although other model such as Izhikevich model that preserves neurocomputational properties do provide attractive alternative, they are not suited for detailed biological studies that require realistic synapses, neuromodulation, and morphology to represent transmission of signals from dendrites to soma and vice versa. We report a procedure to develop a reduced order model which provides a good compromise between biological realism and ease of computation.

To create such reduced order neuron models, we start with morphological data about a neuron or a multi-compartmental model. The passive properties of the cell (e.g., input resistance, time constant, resting potential), known current channel types and their densities, and responses to current injections are then determined from the literature. The reduced order neuron model is developed in a series of steps. We consider reasons why two-compartment models including (soma+axon and dendrite) generally do not satisfy all the key cellular properties. A three-compartment model, on the other hand, may be adequate but may not be able to integrate synaptic inputs on multiple dendrites, particularly from different afferents. Other issues are also considered, including the effect of dendritic v/s somatic inhibition.

A detailed 69compartment model of a lateral amygdala was reduced to both 3- and 4-compartmental models to illustrate the proposed methodology. Examples of principal cells and interneurons from other areas such as the prefrontal cortex are also considered.

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Mechanisms of homeostatic plasticity operate to maintain appropriate network output vital to animal survival. The crustacean cardiac ganglion maintains rhythmic contractions in the crustacean heart using only four pacemaker neurons (small cells) and five motor neurons (large cells). In this system we show two outward potassium currents (\(IA\) and \(IKCa\)) in the “large cell” motor neurons maintain a negative conductance relationship that is vital to the cells’ intrinsic excitability as well as synchronous motor neuron bursting during network output. Disrupting this relationship by selectively decreasing one of the currents results in a rapid homeostatic increase in the other current; this compensation both restores large cell excitability and appropriate network function in 1-2 hours and is at least partially dependent on the calcium activated phosphatase calcineurin. The negative relationship found between \(IA\) and \(IKCa\) currents is in direct contrast to a positive correlation found between single large cell expression of the channel genes responsible for these currents- \(shaker\ (IA)\) and \(BKKCa\ (IKCa)\). This disparity in relationships may indicate how these conductances so rapidly compensate for each other- by having a reservoir of both channel genes readily available while other intracellular mechanisms dictate conductance magnitude. We also investigated the role electrical synapses play while motor neuron bursts are de- and resynchronized after intrinsic currents are altered. These data shed light on how compensatory mechanisms can quickly restore important network function as well as how homeostatic mechanisms affect both intrinsic conductance magnitude and electrical synaptic strength within a network.