Modeling the milk-ejection reflex

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Abstract

We present a model of the bursting behavior observed during lactation in hypothalamic magnocellular neurons releasing the hormone oxytocin (OT). The OT system is modeled as a network of Integrate-and-Fire neurons interacting through dendritic release of OT. Each neuron receives a stochastic synaptic input which is responsible for a tonic background activity, and a suckling-related input which triggers accumulation of a releasable pool of OT in the dendrites (priming). Dendritic priming allows spike-dependent release to occur, thereby switching on communication among neurons. As a result, a synchronised bursting activity is produced in the network, resembling that observed *in vivo*.

Key words: Magnocellular neurons, bursting, dendritic release.

1 Introduction

When pups suckle, they are rewarded with an intermittent let-down of milk that results from reflex release of the hormone oxytocin (OT) from the pituitary gland. OT is synthesized by magnocellular hypothalamic neurons (OT cells), and is secreted from their nerve endings in the pituitary following spike activity. OT cells normally discharge asynchronously at low firing rate, but during suckling, every 5 minutes or so, every oxytocin cell discharge spikes in brief, intense bursts, that result in massive pulsatile release from the pituitary [1]. The milk-ejection reflex was the first example of a physiological role for peptidergic communication within the brain. The reflex is co-ordinated

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through the central release of OT, is facilitated by OT injection into the hypothalamus, and is blocked by injection of oxytocin antagonists [2]. Oxytocin is released not only from nerve endings, but also from OT cells dendrites [6]. During lactation the astroglial architecture of the hypothalamus is reorganized to facilitate dendro-dendritic interactions between OT cells [4]. In the hypothalamus, OT acts on presynaptic nerve endings to inhibit excitatory synaptic input [3]; on glial cells to promote the morphological reorganization that facilitates dendro-dendritic interactions [6], and on oxytocin cells themselves to depolarize them [7], and to attenuate the inhibitory effects of GABA [9]. Recent evidence [5] has shown that OT acts via specific receptors on the oxytocin cells triggering calcium mobilization from thapsigargin-sensitive stores, and making dendritic oxytocin available for subsequent activity-dependent release (priming). Thus dendritic release facilitates further release, and also enhances the excitability of the OT cells. This positive-feedback action is weak under normal conditions, but OT cells dendrites are bundled together in lactating rats, with extensive regions of direct apposition allowing mutual excitatory coupling.
Here we examine whether these experimental findings amount to an explanation for the milk-ejection reflex, by implementing them in a computational model. The OT system is modeled as a network of neurons interacting through the release of OT. Each neuron is endowed with two dendrites where the peptide is continuously stored in response to suckling input, and can be released in response to spike activity and/or increased extracellular OT concentration. Released OT is assumed to excite neighboring cells and to act retrogradely to reduce afferent inputs. Simulation results show that the model is able to reproduce quantitatively all basic features of the milk-ejection reflex, including the duration, intensity, and periodicity of bursts, and the coordination between bursts in different cells.

2 Model description

We considered a network of $n = 15$ neurons, each one endowed with two dendrites, denoted by $(i, 1)$ and $(i, 2)$ for the ith neuron. Dendrites are grouped together in $n_b = 3$ bundles; the sets B_1, B_2, B_3 specify the dendrites contained in each bundle (Fig.1). The dynamics of membrane potential for the ith cell is given by

$$dv_i = -k_1(v_i - v_{\text{rest}})dt + dN_i + I_{OT,i}dt \tag{1}$$

where k_1 is the membrane constant, v_{rest} is the resting potential, $N_i(t)$ is a stochastic process representing the synaptic input, and $I_{OT,i}$ represents the input received from the dendrites. The spike threshold is modeled as $T = T_0(1 + ke^{-t'/\tau})$, where t' is the time from the last spike, T_0 is the observed

threshold, and the parameters k and τ were adjusted to match experimental results. We assume that the local OT concentration inside each bundle, (o_1, o_2, o_3), and the OT concentration in the extracellular fluid of the SON, $\bar{o}$, evolve in time according to the following equations

$$do_k = -k_4 o_k dt + \sum_{i=1}^{n} \sum_{j=1}^{2} C_{i,j}^k dR_i^j - k_5(o_k - \bar{o})dt \tag{2}$$

$$d\bar{o} = -k_6 \bar{o} dt + \alpha \sum_{k=1}^{n_b} k_5(o_k - \bar{o})dt \tag{3}$$

The summation term in Eq. 2 represents the amount of OT released into the k-th bundle from all the afferent dendrites, given the network structure represented by the matrices $C_{i,j}^k = \chi_{\{(i,j)\in B_k\}}$. We assumed that OT is degraded/removed from the bundles with a constant rate k_4, diffuses into the SON with rate k_5, and is degraded/removed in the SON with the rate k_5. The factor α scales the volumes of the bundle and the SON compartments. We hypothesized that OT is continuously accumulated in dendrites in response to the suckling stimulus, so the concentration of OT stored in the jth dendrite of the ith cell, r_i^j, evolves in time according to the following equation,

$$dr_i^j = I_{\text{lac}} dt - dR_i^j \tag{4}$$

where I_{lac} represents the reserve build-up rate during lactation, and

$$dR_i^j = r_i^j \left(k_3 dN_s + k_3' \sum_{k=1}^{n_b} C_{i,j}^k F_2(o_k)dt + k_3'' F_3(f_i) dS_i \right) \tag{5}$$

is the amount of oxytocin released from the dendrite during the time interval dt. In writing Eq. 5 we assumed that a specific synaptic input, modeled here by the Poisson process $N_s(t)$, is activated during suckling, and can directly trigger release from dendrites. Further, we assumed that an increase in OT concentration in the bundles can induce dendritic release through an auto-catalytic process which we modeled by the sigmoidal function F_2. The last term in Eq. 5 accounts for activity-dependent release. To model this, we introduced the process $S_i(t)$, representing the number of spikes generated in the i-th cell for $t' < t$, and the sigmoidal function F_3, which attenuates the release when the recent activity of the cell, f_i, is below a fixed threshold.
The input term $I_{OT,i}$ in (1) is given by $I_{OT,i} = k_2(o_{k_1} \cdot o_{k_2})$, where k_1^i,k_2^i are the indexes of the two bundles where the cell's dendrites are found. Multiplication of the 'OT-signals' received on different dendrites was found to improve synchronization of bursting activity in the network. Finally, the synaptic input is given by $dN_i = F_1(\bar{o})(a_E(v_i - V_E)dN_{E,i} - a_I(v_i - V_I)dN_{I,i})$, where $N_{E,i}$, $N_{I,i}$ are independent Poisson processes of rate λ_E,λ_I, $a_E(-v_{\text{rest}} + V_E)$, $a_I(v_{\text{rest}} - V_I)$ are the magnitude of single EPSPs and IPSPs at the resting potential, and the

sigmoidal function F_1 accounts for a retrograde attenuation of the synaptic input up to 60%, when the OT concentration in the SON is above a fixed threshold.

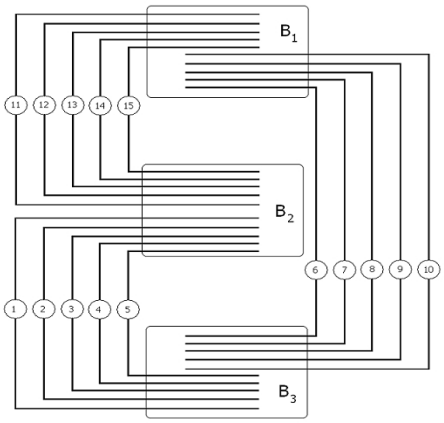

Fig. 1. Schematic drawing of the network setup for $n = 15, n_b = 3$.

3 Simulation results

Fig. 2 shows simulated firing activity in a model cell, in response to the application of the suckling stimulus. Bursts occurred almost periodically, superimposed on a tonic background activity of about 4-5 Hz, they were synchronized across the whole population, and were followed by a period of quiescence lasting up to 14 s. An average delay in burst onset of 0.52 ± 0.24 s has been calculated from data. Greater delays can be observed between cells belonging to different groups, while cells projecting to the same bundles tend to respond in phase due to the common input received on their dendrites. Fig. 3 compares simulated burst profiles and background ISIHs with data recorded *in vivo* from a lactating animal. Burst parameters (duration, amplitude, peak frequency) were found to be in good agreement with experimental data.
Fig. 4 shows that an excess of excitation, simulated by increasing the excitatory input rate, can destroy an ongoing bursting reflex by exaggerating the dendritic reserve depletion rate. This effect highlights the impact of spike-dependent release on the generation of the bursting pattern, and has been observed *in vivo* after application of stimuli that excite the background activity of OT cells. On the other hand, increasing inhibition to counteract over-excitation may restore bursting by keeping the basal firing rate back into an optimal regime. This result is also consistent with the paradoxical observation that application of GABA in the SON inhibits OT cell background activity, yet facilitates milk-ejection burst activity [8].

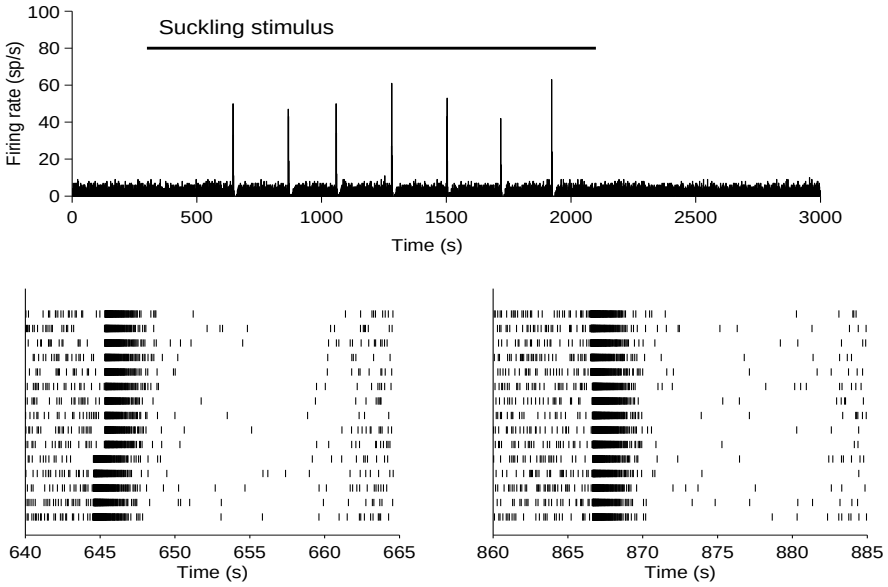

Fig. 2. (Upper panel) Simulated bursting activity in response to suckling stimulus. (Lower panels) Raster plots show synchronisation of bursts over the whole network and post-burst silence periods due to suppression of afferent input by OT.

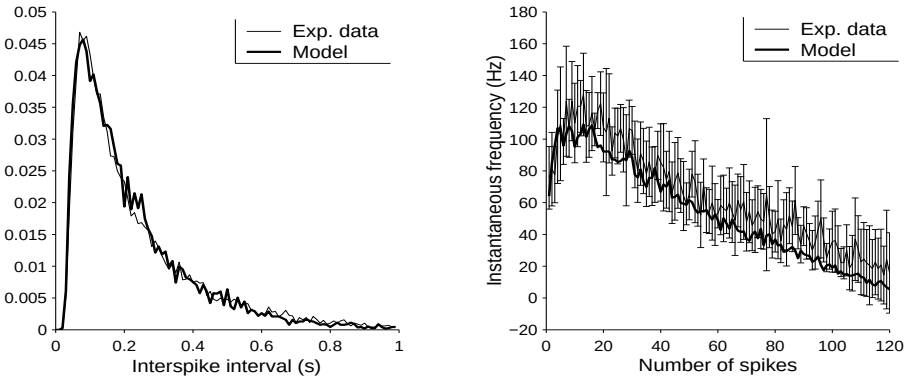

Fig. 3. Comparison of inter-burst ISIHs (left), and burst profiles (right).

4 Conclusions

This study indicates a possible mechanism for burtsting in the OT system based on dendritic release of OT, and dendro-dendritic interactions. A key element is represented by the dendritic stores which act as a capacitative source of excitation, charged up during suckling and discharged abruptly during a burst. The model shows that bursts can originate via a positive feedback of OT on its own release, and that excitation can spread rapidly across the network to produce synchronised activation of all cells. Also, the model explains some unusual features observed in experimental studies, for instance how stimuli that excite the background activity of OT cells tend to suppress the milk-ejection reflex, while transient application of inhibitory stimuli can facilitate bursting.

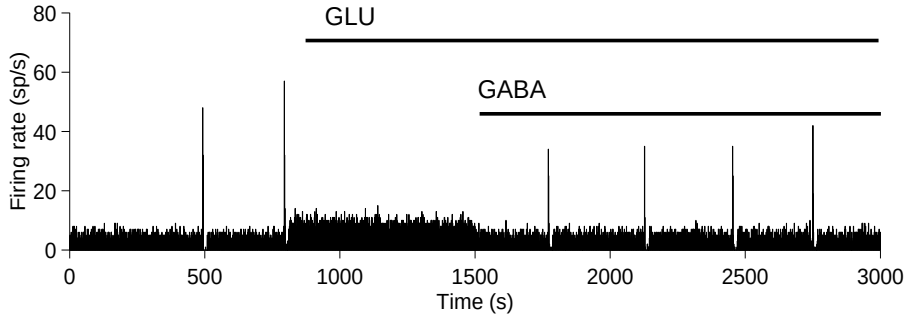

Fig. 4. An ongoing bursting pattern is destroyed by increasing excitatory input ($\lambda'_E = 1.3 \cdot \lambda_E$), and partially restored after increasing inhibitory input ($\lambda'_I = 1.7 \cdot \lambda_I$).

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