Modelling phasic firing in vasopressin neurones

E. Rossoni [a], G. Leng [b], J. Feng [a]

[a] *University of Sussex, Department of Informatics, Brighton BN1 9QH, UK*

[b] *University of Edinburgh, School of Biomedical and Clinical Laboratory Sciences, Edinburgh EH8 9XD, UK*

Abstract

Hypothalamic neurons secreting the hormone vasopressin (VP cells) exhibit a phasic bursting activity crucial for hormonal release. We propose a conductance-based model of a VP cell that reproduces the basic features of phasic bursting as observed *in vivo*. The model includes a nonlinear dynamics for the intracellular Ca^{2+} concentration, which accounts for Ca^{2+}-induced Ca^{2+} release from internal stores (CICR). Results suggest that the observed spike pattern may be due to the interplay between a Ca^{2+}-dependent potassium current and an amplified Ca^{2+} signaling system via CICR.

Key words: Phasic bursting, magnocellular neurons, Ca^{2+} oscillations

1 Introduction

The release of the hormone vasopressin (VP) depends on the pattern of activity of the magnocellular neurosecretory neurons, located in the mammalian hypothalamus [9]. VP is involved in body fluid homeostasis, and is released in response to increased plasma osmotic pressure and reduced plasma volume. At normal plasma osmolarity, VP cells are generally silent or fire slowly and irregularly. When the plasma concentration of Na^{+} rises, VP cells increase their firing rate, and adopt an asynchronous phasic bursting pattern with alternating periods of activity and silence lasting tens of seconds each [4]. This pattern optimises the efficiency of hormonal secretion from nerve terminals [2]. During chronically maintained stimulation, bursts become shorter and more

Email addresses: e.rossoni@susx.ac.uk (E. Rossoni), gareth.leng@ed.ac.uk (G. Leng), jianfeng@sussex.ac.uk (J. Feng).

intense, and their timing becomes more regular [11].
It is now widely recognized that phasic bursting in VP cells is neither a passive response to a phasically patterned input, nor does it reflect spontaneous oscillation of membrane potential, but instead results from the interaction between the synaptic input and an endogenous mechanism [6].
VP cells display long depolarising after-potentials (DAPs) which arise slowly following a spike and increase the likelihood of generating successive action potentials [1]. In phasically active cells, DAPs following consecutive spikes summate temporally into a depolarised plateau potential. Synaptically induced spike activity is believed to trigger and maintain the plateau potential, thus providing a positive feedback mechanism that sustain the burst [7]. Bursts evoked by current injection or by antidromic stimulation are followed by an activity-dependent after-hyperpolarisation (AHP) which mainly results from a slow, apamin-sensitive Ca^{2+}-dependent K^+-current ($I_{K(Ca)}$), and functions as a feedback inhibitor of spike activity. During the course of a burst, increasing intracellular Ca^{2+} concentration progressively activates $I_{K(Ca)}$, thereby reducing the plateau potential.
Growing evidence [10] has made it possible to propose the hypothesis that the subcellular process of Ca^{2+}-induced Ca^{2+} release from the intracellular stores (CICR) could be involved in the process of excitation-secretion coupling of VP cells, via a recruitment of Ca^{2+}-dependent K^+ channels. Here we show how the interplay between a Ca^{2+}-dependent K^+ current and of a nonlinear calcium dynamics, can account for the generation of phasic activity in a simple neuronal model. In particular, the inactivation of $I_{K(Ca)}$ is suggested to be responsible for the burst onset, whereas burst termination and prolonged inter-burst intervals are due to the strong activation of $I_{K(Ca)}$ following large intracellular Ca^{2+} oscillations mediated by CICR.

2 Model

The model consists of a single isopotential compartment. The dynamics of the membrane potential, V, is given by the following equation:

$$C_m \frac{dV}{dt} = -I_{Na} - I_K - I_{K-Ca} - I_{Ca,L} - I_{Ca,T} - I_L - I_{syn} - I_{osm} \qquad (1)$$

where C_m is the membrane capacitance. Ionic currents in the model include: a fast inward Na^+ current (I_{Na}), a delayed rectifier K^+ current (I_K), a Ca^{2+}-dependent K^+ current (I_{K-Ca}), a low-voltage activated Ca^{2+} current ($I_{Ca,T}$), a high-voltage activated Ca^{2+} current ($I_{Ca,L}$), and a leakage current (I_L). The osmotic stimulus has been modelled by a voltage-independent inward current, I_{osm}, which represents the effect of stretch-sensitive cation channels [3]. The

synaptic input, I_{syn}, is modelled by the sum of two independent Poisson processes producing randomly occurring excitatory and inhibitory post-synaptic potentials; following [8], a balanced synaptic input has been considered. Voltage dependent ionic conductances are modelled using the Hodgkin-Huxley formalism.
The Ca^{2+} concentration in the free intracellular space ($[Ca^{2+}]_i$), and inside the endoplasmatic reticulum ($[Ca^{2+}]_{ER}$) are described by the following balance equations

$$\begin{cases} \frac{d[Ca^{2+}]_i}{dt} = F_0 + F_1 I_{Ca} + F_{ER,leak} - F_{SL,pump} + F_{ER,rel} - F_{ER,pump} \\ \frac{d[Ca^{2+}]_{ER}}{dt} = F_{ER,pump} - F_{ER,rel} - F_{ER,leak} \end{cases} \quad (2)$$

where F_0 represents a constant Ca^{2+} entry into the cell body; F_1 scales the total calcium current, I_{Ca}, into a flux rate; $F_{ER,leak}$ represents the leakage from the internal stores, and $F_{SL,pump}$ describes the pumping into the extra-cellular space. The terms $F_{ER,rel}$ and $F_{ER,pump}$ represent the Ca^{2+}-induced release from the stores, and the pumping into the stores, respectively, and are modelled as in [5].

3 Results

The model cell has a resting potential of -63 mV and a spike threshold of -55 mV. Individual spikes are followed by a brief HAP of about 6 mV amplitude, and a DAP of 2 mV amplitude, which lasts for about 300 ms. Phasic bursting is observed in response to steady osmotic stimulation and stationary synaptic input (Fig. 1). At low input level, the cell fires slowly and irregularly. Clear bursting activity emerges as the rate of the synaptic input is increased. At higher input rates, or in the presence of increased osmotic stimulation, the cell tends to fire continuously, and the phasic pattern is progressively lost. Bursts of spikes last from tens of seconds up to 4-5 minutes, and are separated by silent intervals from 2-5 s up to 40 s, depending on the rate of synaptic input and the magnitude of the applied current.
The intracellular Ca^{2+} concentration exhibits large oscillations synchronized with phasic bursts (Fig. 2). During a burst, low-amplitude fluctuations in $[Ca^{2+}]_i$ result from spike induced Ca^{2+} entry through voltage-gated channels, and a slow drift in $[Ca^{2+}]_i$ is apparent. As soon as $[Ca^{2+}]_i$ reaches a threshold concentration, the CICR becomes regenerative, and a rapid rise in $[Ca^{2+}]_i$ is produced which fully activates $I_{K(Ca)}$. This results in burst termination, followed by a prolonged AHP. The excess in $[Ca^{2+}]_i$ is then gradually cleared during the silent phase. Finally, as $[Ca^{2+}]_i$ returns to its baseline, $I_{K(Ca)}$ gets inactivated, and the cell can start firing again.

Electrical stimuli applied to the neural stalk evoke spikes in VP cells via antidromic propagation of axonal spikes into the cell bodies. Experimental studies have shown that brief trains of antidromic spikes can trigger full bursts of spikes in VP cells, and equally can stop established bursts [7]. On the other hand, low-frequency antidromic spikes produce the interesting effect that cells appear to compensate for the additional evoked spikes by a matching reduction in spontaneous discharge. VP cells thus appear to 'defend' their firing rate against perturbations. Since antidromic activation mimics particular effects of synaptic excitation, one may infer that an increased frequency of excitatory

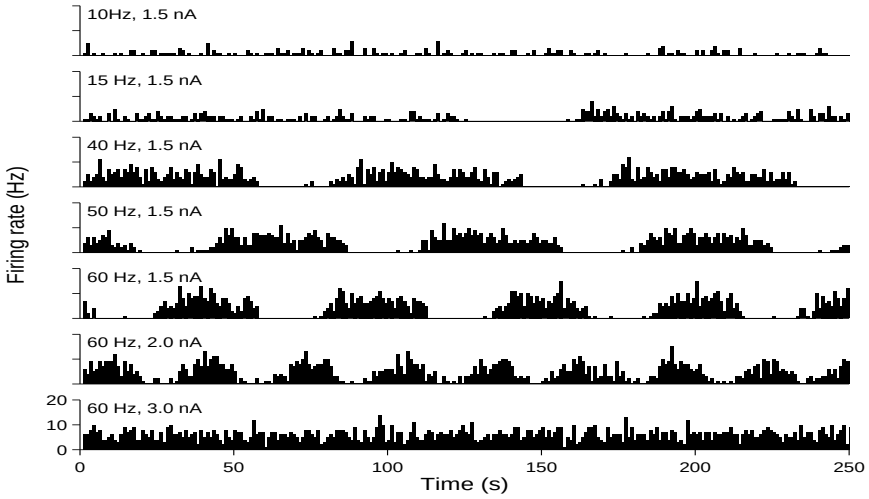

Fig. 1. Phasic bursting in the model. The synaptic input rate (λ_{syn}) and the amplitude of the osmotic stimulation are reported in the legend. Spike activity is averaged over 1 s bins.

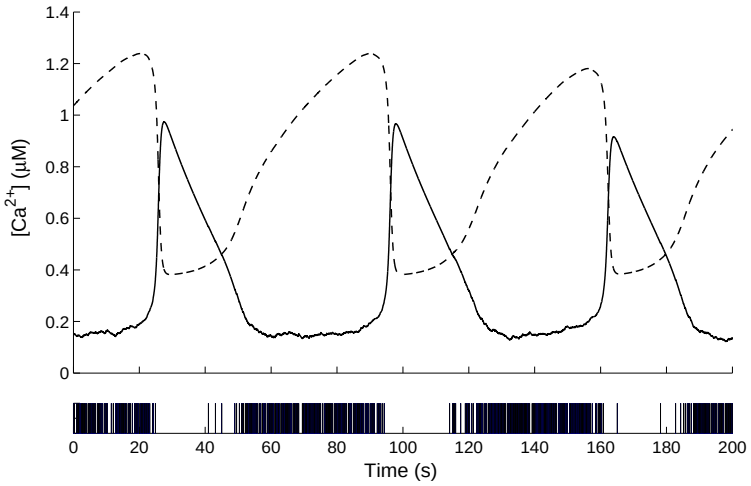

Fig. 2. Time courses of Ca^{2+} concentration in the intracellular space (solid line) and inside the ER (dashed line) during simulated phasic activity (λ_{syn} = 50 Hz, I_{osm}=1.5 nA); below a schematic of spike activity.

input might trigger a burst if a VP cell is silent, stop a burst if a cell is active, or have no effect if the stimulus is week enough to allow the cell to defend its firing rate effectively.
Simulation results show that a transient increase in the frequency of the excitatory input can trigger a full burst if the cell is inactive and it is not in the refractory state just after a burst (Fig. 3). Also, a flurry of EPSPs may stop an ongoing burst if the consequent increase in $[Ca^{2+}]_i$ is large enough to elicit CICR, but may fail to stop the burst if the stimulus is delivered soon after the beginning of a burst, when the internal Ca^{2+} are not yet fully replenished.

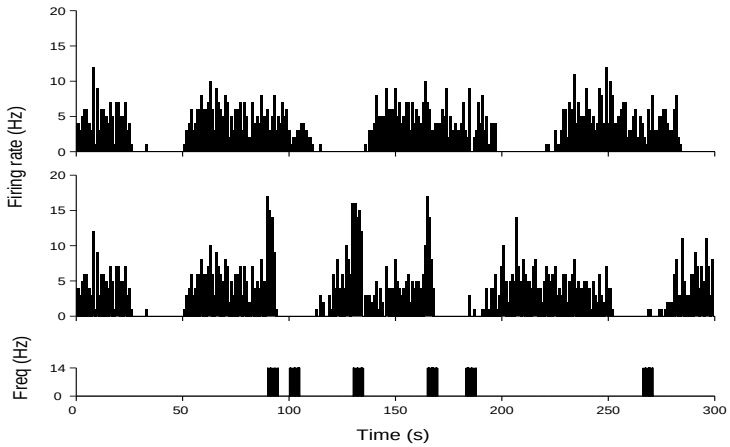

Fig. 3. Phasic activity under control condition (upper panel; $\lambda_{syn} = 40$ Hz, I_{osm}=1.5 nA), and after additional afferent stimulation (middle panel). Lower panel is a schematic of the applied stimulus. Each afferent stimulus consists of a train of spike-eliciting current pulses delivered at 14 Hz for 5 s.

4 Conclusion

We have presented a mathematical model which mimics the behaviour of VP cells under physiological circumstances. The introduction of a Ca^{2+} dynamics allowed us to delineate a mechanism through which oscillations between phases of silence and activity are made possible. Ca^{2+} entry through voltage-gated channels, Ca^{2+} release from internal stores, Ca^{2+} sequestration into the endoplasmatic reticulum and pumping into the extra-cellular space, have been found to combine to generate large oscillations in $[Ca^{2+}]_i$. These lead a strong activation of $I_{K(Ca)}$, thereby switching the cell from the active to the silent state. On the other hand, burst onset is obtained in the model as a result of $I_{K(Ca)}$ inactivation, following the decay of Ca^{2+} transients. The model also show how bursts of activity in VP cells can be both triggered or truncated by a transient flurry of EPSPs.

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References

[1] W.E. Armstrong, B.N. Smith, M. Tian. Electrophysiological characteristics of immunochemically identified rat oxytocin and vasopressin neurones *in vitro*. J. Physiol. (Lond.) 475 (1994) 115 - 128.

[2] R.J. Bicknell, G. Leng. Relative efficiency of neuronal firing patterns for vasopressin release in vitro. Neuroendocinology 33 (1981) 295 - 299.

[3] C.W. Bourque, S.H. Oliet. Osmoreceptors in the central nervous system. Ann. Rev. Physiol. 59 (1997) 601 - 619.

[4] M. Brimble, R.E. Dyball. Characterization of the responses of oxytocin- and vasopressin-secreting neurones in the supraoptic nucleus to osmotic stimulation. J. Physiol. (Lond.) 271 (1977) 253 - 271.

[5] A. Goldbeter, G. Dupont, M.J. Berridge. Minimal model for signal-induced Ca^{2+} oscillations and for their frequency encoding through protein phosphorylation. Proc. Natl. Acad. Sci. USA 87 (1990) 1461 - 1465.

[6] G.I. Hatton, Z. Li. Mechanisms of neuroendocrine cell excitability, in: H.H. Zingg, D.G. Bichet, C. Bourque, eds., Vasopressin and Oxytocin: Synopsis of Recent Advances in Molecular, Cellular and Clinical Research. (Plenum Press, New York, 1998) 79 - 95.

[7] G. Leng, R.E. Dyball, S.M. Luckman. Mechanism of vasopressin secretion. Horm. Res. 37 (1992) 33 - 38.

[8] G. Leng, C.H. Brown, P.M. Bull, D. Brown, S. Scullion, J. Currie, R.E. Blackburn-Munro, J. Feng, T. Onaka, J.G. Verbalis, J.A. Russell, M. Ludwig. Responses of magnocellular neurons to osmotic stimulation involves co-activation of excitatory and inhibitory input: an experimental and theoretical analysis. J. Neurosci. 21 (2001) 6967 - 6977.

[9] D.A. Poulain, D. Brown, J.B. Wakerley. Statistical analysis of patterns of electrical activity in vasopressin- and oxytocin-secreting neurones, in: G. Leng, ed., Pulsatility in Neurosecretory Systems (CRC Press, 1988) 119 - 154.

[10] M. Tanabe, B.H. Gähwiler, U. Gerber. L-type Ca^{2+} channels mediate the slow Ca^{2+}-dependent afterhyperpolarization current in rat CA3 pyramidal cells *in vitro*. J. Neurophysiol. 80 (1998) 2268 - 2273.

[11] J.B. Wakerley, D.A. Poulain, D. Brown. Comparison of firing patterns in oxytocin- and vasopressin releasing neurones during progressive dehydration. Brain Res. 148 (1978) 425 - 493.