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Information coding in vasopressin neurons—The role of asynchronous bistable burst firing

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ABSTRACT

The task of the vasopressin system is homeostasis, a type of process which is fundamental to the brain's regulation of the body, exists in many different systems, and is vital to health and survival. Many illnesses are related to the dysfunction of homeostatic systems, including high blood pressure, obesity and diabetes. Beyond the vasopressin system's own importance, in regulating osmotic pressure, it presents an accessible model where we can learn how the features of homeostatic systems generally relate to their function, and potentially develop treatments. The vasopressin system is an important model system in neuroscience because it presents an accessible system in which to investigate the function and importance of, for example, dendritic release and burst firing, both of which are found in many systems of the brain. We have only recently begun to understand the contribution of dendritic release to neuronal function and information processing. Burst firing has most commonly been associated with rhythm generation; in this system it clearly plays a different role, still to be understood fully.

1. Introduction

We now recognise that rather than just simple integrators and relays of activity, most neurons have complex pattern generating properties. An important question in contemporary neuroscience is how these properties contribute to information processing (Ramirez et al., 2004; Buzsáki and Draguhn, 2004). In particular, many neurons generate "bursting" patterns of electrical activity, arising either through intrinsic mechanisms, or via network interactions. Some of these contribute to generating physiological rhythms (such as the respiratory rhythm, Del Negro et al., 2002), where neurons synchronise across a network to generate an emergent rhythm. In others, single synchronised bursts are essential to the physiological output, such as oxytocin cells driving the periodic milk let-down during suckling (Rossoni et al., 2008). However, some neurons, like the vasopressin cells of the hypothalamus, generate bursting activity individually (Fig. 1), and fire *asynchronously* (Leng et al., 2008), such that the bursting is not reflected in the population output – so what is *this* bursting behaviour for? We know in vasopressin neurons that bursts are efficient for stimulus-secretion coupling, optimising secretion per spike, but it is not clear why this is important – many neurons fire spontaneously at much higher rates than vasopressin cells. Moreover, bursting in these cells is efficient for triggering secretion only because of particular properties of their axon terminals, indicating that these secretion properties have co-evolved with the bursting behaviour; suggesting that bursting is important for other reasons. Because bursting is such a widespread feature in the CNS, arising in many different ways, we believe it is important to understand exactly what advantages it offers for information processing.

Vasopressin and its control of osmotic pressure is a relatively simple and very well studied system. It presents an unusually strong opportunity to be able to relate information processing properties of cells to their physiological function as part of a system. We are currently attempting to apply a modelling and complex systems approach, in order to test specific hypothesis about the adaptive value of its particular features (heterogeneity, bistability, autocrine and paracrine communication mechanisms). We will test these features ultimately by expressing the physiological function of the system in terms of a defined control task, integrating neuronal modelling into a physiological systems model. The project is defined in three parts:

1. Build a single neuron model, including spike firing, vasopressin secretion and intercellular communication mechanisms.
2. Duplicate the model to build a network. Evaluate input/output characteristics and study the effects of varied assumptions about communication.
3. Build a closed-loop system model and use this to test varied network models, comparing their performance in matching

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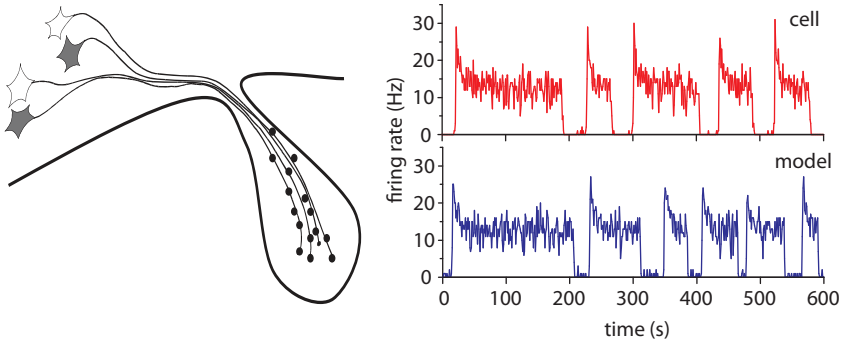

Fig. 1. Vasopressin cells project to the posterior pituitary. In response to osmotic input, cells fire in a distinct phasic bursting pattern. We can closely match this behaviour with a relatively simple single cell model.

experimental data, and systematically evaluate network performance, robustness and efficiency.

The first details of these components are presented elsewhere (Clayton et al., 2010). What we seek to develop here is the rationale and strategy behind the work. Though these parts require initially to be developed in sequence, they will continue to be refined in parallel, better informed by their role and behaviour as part of a system. This is an extended version of a paper previously presented at the 9th International Conference on Information Processing in Cells and Tissues (MacGregor et al., 2012).

2. Background: homeostatic role of vasopressin

Vasopressin is made by neurons of the supraoptic and paraventricular nuclei of the hypothalamus, and is secreted into the blood from axonal terminals at the posterior pituitary. This is a very important "model system" in neuroscience for many reasons, including the large size and accessibility of the neurons, and the fact that, because these neurons secrete their products at measurable amounts into the systemic circulation, their electrical activity can be directly related to secretion and physiological function. These cells use cell volume modulated stretch-sensitive channels to respond to osmotic pressure, and also receive synaptic input from other osmosensitive neurons (Bourque, 2008).

Vasopressin cells display relatively long bursts and silences. They are bistable oscillators; small perturbations can "flip" a neuron from either state (burst or silence) to the other, because their intrinsic activity-dependent conductances can either stop or start a burst. An asynchronously firing population of vasopressin cells has a lot of potential for interesting signal processing properties. They may act as a low-pass filter – preserving low frequency signals while filtering out stochastic noise in their inputs (Sabatier and Leng, 2007). While individual neurons respond erratically to acute changes, the asynchronicity means that these erratic responses are smoothed out. The vasopressin cells are also a heterogeneous population; variation in expression of membrane channels, receptors, and synaptic input, produce differing sensitivities to osmotic pressure and a wide spectrum of bursting behaviour. This heterogeneity has been preserved through evolution, suggesting either that it is an inescapable limitation, or, more interestingly, that the heterogeneity is adaptive and has some functional purpose. There are some clear functional consequences of heterogeneity – a population that is heterogeneous in osmotic responsiveness will have a wider dynamic range than a homogeneous population. But there are also costs; for example, a homogeneous population has a high intrinsic redundancy, so it is robust to degradation. A heterogeneous population will generally be less robust – unless the heterogeneity is not hard-wired, but arises from network self organisation. The most obvious way that heterogeneity could be self-organised would be if individual neurons cycle through phases of varying osmotic responsiveness – as we have suggested that they might (Leng et al., 2008). The population of vasopressin neurons acts together as a complex system, with multiple feedbacks acting at different levels, including autocrine signals and paracrine signalling between cells. These properties co-ordinate the vasopressin cells, presumably to optimise emergent features of system behaviour.

The vasopressin-osmotic system is part of a larger homeostatic system that regulates plasma volume and electrolyte concentration via many mechanisms (including thirst and natriuresis; see Bie, 2009). Vasopressin secretion (Fig. 2) increases linearly with osmolarity above a set point (Dunn et al., 1973), and this is essential for regulation of plasma volume and osmolarity. Plasma osmolarity is normally regulated to within a few percent, so vasopressin cells, as a population, must respond reliably to a change in extracellular $[Na^+]$ of just ~1 mM – tiny compared to the fluctuations expected as the result of stochastic variations in neuronal activity. A sustained increase in osmolarity requires a sustained vasopressin response, so the vasopressin cell population must maintain their response to an unvarying input signal. Most neurons are good at responding to change, but to do this they adapt to a constant signal; vasopressin cells as a population must not adapt to sustained osmotic stimulation.

At normal osmotic pressures, the cells fire slowly; each secretes just 1–2 vesicles/s, but this is enough to maintain normal circulating concentration of ~1 pg/ml (see Leng and Ludwig, 2008 for details). As osmotic input increases, the cells enter a bistable phasic firing mode (Sabatier and Leng, 2007), consisting of alternating bursts and silences. Each burst typically lasts for 20–60 s at 4–10 spikes/s. Secretion is facilitated by high frequency spiking, but fatigues within about 20 s; this fatigue is reversed after 20–30 s of quiescence; thus a phasic firing pattern optimises secretion per spike (Bicknell, 1988). A burst of ~400 spikes in one vasopressin cell releases about one vesicle from each of its ~2000 nerve endings. However, with chronic stimulation, the stores of vasopressin are progressively depleted; if rats are given 2% NaCl to drink, then stores decline to ~15% of control values over 12 days, despite a massive increase in synthesis (Kondo et al., 2004). This decline reflects the delay between increasing the rate of synthesis and replenishment of the stores. At any particular time, hormone secretion in response to a given stimulus is proportional to the size of the store (Higuchi et al., 1991); thus, during progressive dehydration, spike activity becomes less and less effective at secreting vasopressin.

The larger homeostatic system, of which the vasopressin system is part, must regulate plasma osmolarity and volume within strict tolerance. Both hyper- and hyponatraemia are life-threatening outside critical limits. We propose that the utility of this system should be judged not by how accurately it maintains normal osmolarity, but by how well it can prolong survival – *i.e.*, when subject