Excitable Bursting in the Rat Neurohypophysis

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The hormone vasopressin (AVP) regulates:

- blood osmolality (blood concentration)
- blood pressure
- kidney function
- liver function

Secretion increases during dehydration – mediated by a net depolarization of the cell.
AVP/OT
Neurohypophysis
(Posterior Pituitary)
Pituitary
Stalk
Supraoptic and
Paraventricular Nuclei

Supraoptic and
Paraventricular Nuclei

Pituitary Stalk

Neurohypophysis
(Posterior Pituitary)
Hypothalamus

Dendrites
Soma
Axon
Capillary

Pituitary

Hormone Release
Somato-dendritic secretion of autocrine and paracrine messengers

Dynorphin

Vasopressin

Capillary

Hormone Release
Autoregulatory somato-dendritic release

Dynorphin
 AVP

k-receptor

Binding

Internalization

Unbinding

Docking and Release

V1-A receptor

Dense Core Granule

AVP-Dynorphin

Unbinding

Docking and Release

Dense Core Granule
**Basal firing** is *slow-irregular*

- Poisson distributed spike train
- Spikes evoked by random synaptic input
- Firing rate $\leq 1.5$Hz

- Each spike triggers secretion of AVP into the blood
Dehydration alters the firing pattern

**Transient Response**

- **Slow Irregular** (<1.5Hz)
  - AVP cells switch to a *phasic* pattern

- **Fast Continuous** (>3Hz)
  - under extreme stress, AVP cells further switch to *fast-continuous*
  - single, non-repeating bursts can be evoked in *slow-irregular* AVP cells

- **Phasic** (>3Hz)
  - Increasing Stress

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Ionic Currents

Trans-membrane currents mediated by voltage and/or calcium sensitive ion channels
Mathematical Model

Hodgkin-Huxley type system with a simple calcium dynamics

\[-C \frac{dV}{dt} = \overbrace{I_{Na} + I_{Ca} + I_A + I_K + I_C}^{\text{Spiking Currents}} + \underbrace{\overbrace{I_{\text{leak}}} \quad \overbrace{I_{\text{syn}}}}_{\text{Reset Currents} \quad \text{Synaptic Input}} \]

\[
\frac{d[Ca^{2+}]_i}{dt} = \alpha I_{Ca}(t) - \gamma ([Ca^{2+}]_i - [Ca^{2+}]_{rest})
\]
The DAP

Each evoked spike is followed by a transient depolarization (DAP)

which depends on calcium

$\tau = 1.851$

$\tau_f = 0.165$

$\tau_s = 1.683$
Modelling the DAP

\[ I_{\text{leak}} = I_{K,\text{leak}} + I_{Na,\text{leak}} \]

We model (Li and Hatton, 1997) the DAP by a transient (\(V\)- and) \(Ca^{2+}\)-dependent modulation of a persistent potassium current: \(I_{K,\text{leak}}\)

\[ I_{K,\text{leak}} = (1 - R) G_{K,\text{leak}} (V - E_K) \]

\[ R \]

\[ [Ca^{2+}]_i \]

\[ I_{K,\text{leak}} = \text{max} \]

Increasing Calcium

\[ I_{K,\text{leak}} = 0 \]

\[ [Ca^{2+}]_i \]
Comparing DAP’s from experiment and model
Multiple DAP’s summate to a plateau that is above spike threshold:

and such plateaus sustain phasic bursts
Calcium

- Reaches a plateau early in the burst
- Remains elevated until burst terminates
AVP cells secrete an opioid – dynorphin – from their dendrites.

Dynorphin inhibits AVP cell activity.

Propose that effects of dynorphin increase during active phase and clear during silent phase.
Dynorphin agonists (U50-3):

- Inhibit the DAP
- Prevent bursting (Brown et al., 1999)

Dynorphin antagonists (BNI):

- Prolong durt duration (Brown, 1999)
HOW does dynorphin act?

- **We propose** that dynorphin shifts the half-activation of $R$ to higher $\text{Ca}^{2+}$ concentrations

- **Thus** raising the plateau threshold while leaving $[\text{Ca}^{2+}]_i$ unchanged

- **Eventually** plateau can no longer support spiking and cell falls silent – burst terminates
Increasing

Decreasing

Both

Increasing $[\text{Ca}^{2+}]_i$

Decreasing $[\text{Ca}^{2+}]_i$

(Burst terminates)

(Slow depolarization)

$[\text{Ca}^{2+}]_i$

($Post$-$Burst$)

$DAP$

$D$

$R$

$R$

$R$

$R$
Dynamics of dynorphin and the $\kappa$-receptor

- $D$ is augmented by $\Delta$ when the cell fires the $i^{th}$ spike (say at time $T_i$)
- $D$ decays exponentially between spikes

$$\frac{d}{dt}D = \Delta \delta(t - T_i) - \frac{1}{\tau_D}D \quad \Delta = \text{constant}$$

Upregulation of the $\kappa$-receptor

Propose that $\Delta$ increases as a function of $D$

$$\frac{d}{dt}D = \Delta \delta(t - T_i) - \frac{1}{\tau_D}D \quad \Delta(D) = \Delta_0 + \epsilon D$$

- **Interpretation:** dynorphin upregulates $\kappa$-receptor density
Comparisons between real and model bursts

![Graphs showing comparisons between real and model bursts.](image)
If cell depolarized far enough...

...phasic activity
Analysis: the *Fast/Slow* reduction

To analyze the phasic model – first split into *fast* and *slow* components

- **fast**: the spiking currents – $I_{Na}$, $I_{Ca}$, $I_{K}$, $I_{A}$, $I_{c}$
- **slow**: the plateau oscillation – $[Ca^{2+}]_i$ and $D$
Spiking currents \( (I_{\text{spike}}) \) pass through saddle-node bifurcation as plateau amplitude increased:
Dissociation of *SLOW* from *FAST* nontrivial:

...the two subsystems are not autonomous

Instead write *SLOW* as a firing rate model and decouple subsystems with this *ansatz*

\[
\frac{d}{dt} C = \nu(R) \Delta C_a - \frac{1}{\tau_{C_a}} (C - C_r) \\
\frac{d}{dt} D = \nu(R) \Delta D - \frac{D}{\tau_D}
\]
Empirically $\nu$ can be fit to

$$\nu = \begin{cases} 
0 & R \leq R_{\text{thresh}} \\
\Gamma (R - R_{\text{thresh}}) & R > R_{\text{thresh}}
\end{cases}$$
and $R_{\text{thresh}}$ is a linear function of $I_{\text{osm}}$.
Nullclines

(i) $I_{app} = 0.0$

(ii) $I_{app} = 3.0$

(iii) $I_{app} = 5.5$
Sub-threshold behaviour

Excitable Bursting – $I_{app} = 0$

- Stable fixed point at $D = 0$ and $[Ca^{2+}]_i = [Ca^{2+}]_{rest}$.
- System is excitable – single oscillations can be evoked by moving the system above threshold ($\Delta Ca^{2+} > 30\text{nM}$).

- Single oscillations are equivalent to evoked bursts in the full model.
- Threshold is close to the calcium influx due to 3 spikes.
Super-threshold behaviour

If the applied current ($I_{\text{app}}$) is increased above threshold, then the fixed point loses stability and the system starts to oscillate – phasic activity.
Firing transitions

- stable steady state $\Rightarrow$ phasic oscillation:
  
  \[ \text{slow irregular} \Rightarrow \text{phasic} \Rightarrow \text{saddle-node bifurcation} \]

- phasic oscillation $\Rightarrow$ stable steady state:
  
  \[ \text{phasic} \Rightarrow \text{fast continuous} \Rightarrow \text{Hopf Bifurcation} \]
Conclusions

We have constructed the first qualitative and quantitative model of the electrical activity of vasopressin MNC’s.

We propose that phasic activity must be driven by an auto-regulatory mechanism, and that dynorphin/κ-opioid receptor secretion is a likely candidate for this mechanism.

Our model reproduces:

- single spikes, basal firing and the fine structure of bursts
- the sequence of firing patterns observed during physiological stress
- (the transient discharge that occurs during sudden stress)

We have also shown that the cells have both excitable and phasic bursting modes: possibly explaining the difference between in vivo and in vitro recordings.
Collaborators

Theory

Arthur Sherman
John Naradzay (UBC)

Experimental – University of Tennessee, Memphis

Bill Armstrong
Joseph Callaway (calcium imaging)
Ryoichi Teruyama (electrophysiology)
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