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A Hodgkin-Huxley type model of subfornical organ neurons

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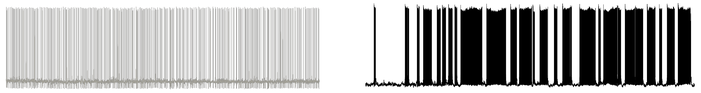
Background

- Subfornical organ (SFO) neurons exhibit a heterogeneity in their expression of ionic currents, spiking behaviour, and response to circulating peptide signals.
- The two prominent spiking behaviours exhibited by SFO subpopulations:

Tonic Firing **Bursting**



- Our lab studies angiotensin II (ANG) and tumor necrosis factor alpha (TNFα); two signaling peptides implicated in hypertension via their influences on SFO neurons.
- Insight into the mechanisms behind SFO neuron heterogeneity is critical for understanding the SFO's role in both hypertension and overall autonomic regulation, but is currently lacking due to limitations in patch-clamp techniques.

Goal

1. Build single-neuron models to account for and explain the behaviour of tonic firing and bursting neurons in the SFO.
2. Implement these models to make predictions about the response of SFO neurons to various circulating peptides, like ANG and TNFα.

Methods & Results

Analysis of spiking behaviour and membrane potential

A. Spike Train Variability (CV)

Calculate interspike intervals (ISI):

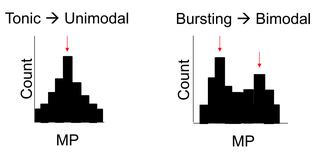
$$ISI = t_i - t_{i-1}$$

Calculate coefficient of variation (CV):

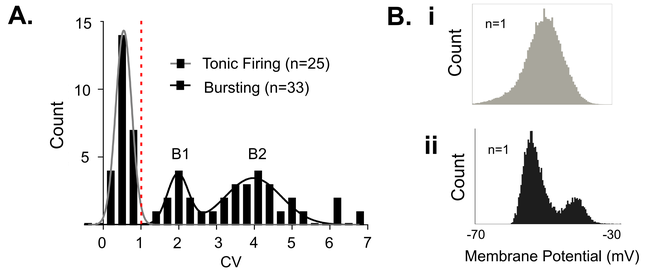
$$CV = \frac{std\ (ISI)}{mean\ (ISI)}$$

B. Membrane Potential (MP) Distribution

Tonic → Unimodal Bursting → Bimodal



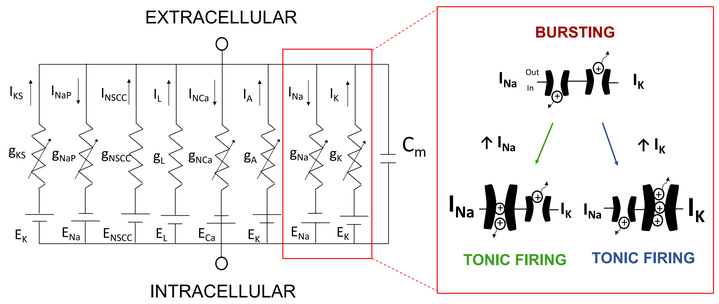
SFO neurons can be classified based on spiking behaviour and membrane potential.



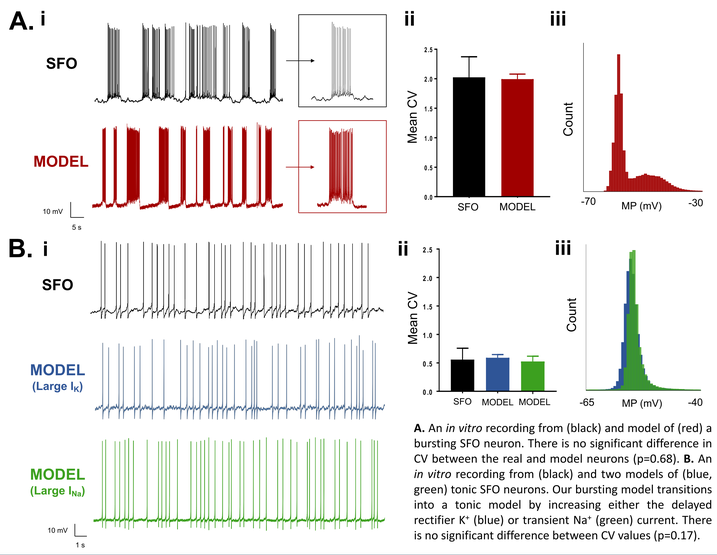
A. Histogram shows the distribution of spike train variability (CV) of SFO neurons (n=58). Tonic firing SFO neurons had a CV < 1, whereas bursting neurons had a CV ≥ 1 and were divided in two subpopulations, B1 and B2. **B.** Histograms represent two single membrane potential distributions of SFO neurons. Tonic firing (i) and bursting neurons (ii) had unimodal (grey) and bimodal (black) distributions, respectively.

Methods & Results (cont.)

Hodgkin-Huxley neuron model

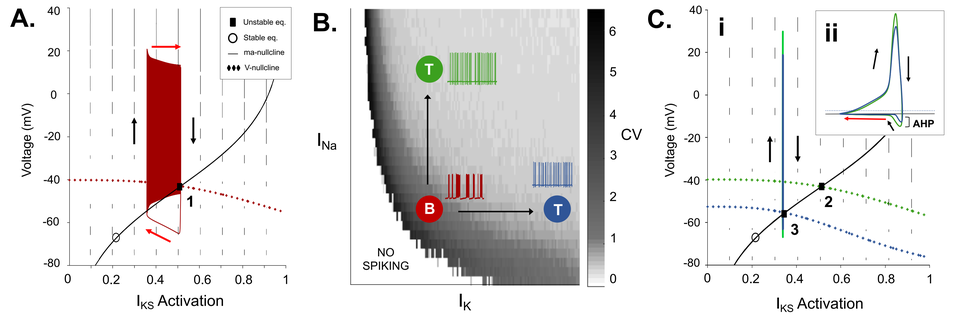


Our model can account for the spike train variability and membrane potential distribution of both SFO subpopulations.



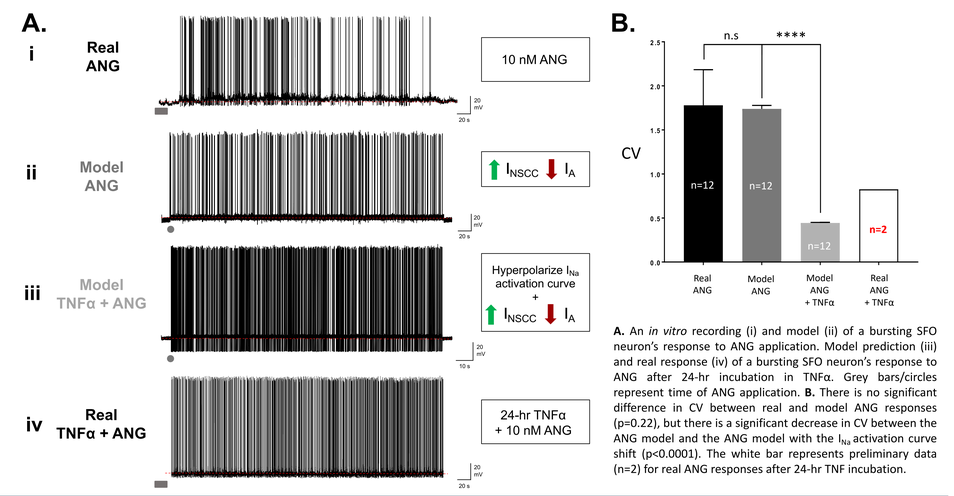
A. An *in vitro* recording from (black) and model of (red) a bursting SFO neuron. There is no significant difference in CV between the real and model neurons (p=0.68). **B.** An *in vitro* recording from (black) and two models of (blue, green) tonic SFO neurons. Our bursting model transitions into a tonic model by increasing either the delayed rectifier K^+ (blue) or transient Na^+ (green) current. There is no significant difference between CV values (p=0.17).

Activation of the slow K^+ current allows for bursting in our model. Increasing the transient Na^+ or delayed rectifier K^+ current results in tonic firing.



A. The slow K^+ current (I_{KS}) activation vs. voltage (V) phase plane for the bursting model. Solid dark red trajectory shows a limit cycle containing a single burst. Red and black arrows show direction of slow and fast movement, respectively. **B.** Size of transient Na^+ (I_{Na}) and delayed-rectifier K^+ (I_K) currents modulate spike train variability (CV). **C.** I_{KS} activation vs. V phase plane for the tonic models. Solid green and blue trajectories each show a limit cycle containing a single action potential.

Our model predicts that 24hr incubation in tumor necrosis factor alpha (TNFα) will potentiate an SFO neuron's response to angiotensin II (ANG).



A. An *in vitro* recording (i) and model (ii) of a bursting SFO neuron's response to ANG application. Model prediction (iii) and real response (iv) of a bursting SFO neuron's response to ANG after 24-hr incubation in TNFα. Grey bars/circles represent time of ANG application. **B.** There is no significant difference in CV between real and model ANG responses (p=0.22), but there is a significant decrease in CV between the ANG model and the ANG model with the I_{Na} activation curve shift (p<0.0001). The white bar represents preliminary data (n=2) for real ANG responses after 24-hr TNF incubation.

Conclusions

1. SFO spiking behaviour can be classified based on the spike train variability and membrane potential.
2. Our model is able to account for the two prominent behaviours exhibited by subpopulations of SFO neurons.
3. Our model predicts that tonic firing SFO neurons may lack sufficient slow K^+ dynamics that are required for bursting behaviour.
4. We can use the bursting model to accurately simulate a real SFO neurons response to ANG and further investigate the integration of ANG with other autonomic signals.
5. Our model predicts that 24-hr incubation with TNFα will potentiate an SFO neurons response to ANG.

Future Research: Investigation into the slow K^+ dynamics of SFO neurons needs to be done. Additionally, further analysis of the integration of TNFα and ANG signals is vital in understanding the SFO's role in hypertension. These models have future application in predicting the integration of various other autonomic signals within the SFO.

Acknowledgements

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