Oxytocin single neuron dynamics. From a complete mathematical model to biological predictions.

Jorge Maícas Royo, Duncan J. MacGregor and Gareth Leng

Centre for Integrative Physiology, University of Edinburgh, UK

Here we show a mathematical model that mimics the spiking and secretory behavior of oxytocin neurons.

Spiking Model

Every oxytocin neuron receives hundreds of input signals that produce presynaptic potentials (PSPs). Excitatory PSPs increase its membrane potential (*Vm*), and inhibitory PSPs reduce it. The model assumes that these arrive randomly at some given rate.

The sum of PSPs (*Vsyn*) is added to the membrane resting potential (*Vrest*). When that addition reaches a *Vthreshold*, a spike is produced and the oxytocin neurone membrane reacts with a **HAP** and an **AHP.**

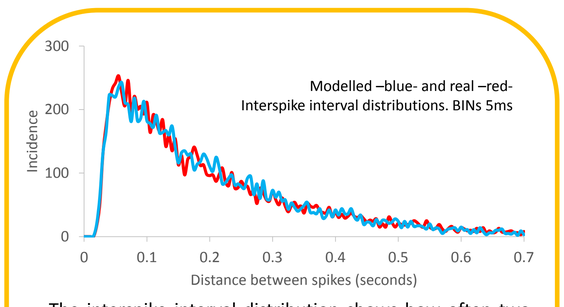
$$V_m = V_{rest} + V_{syn} - HAP - AHP$$

HAP: A single spike is enough to deeply hyperpolarize the cell

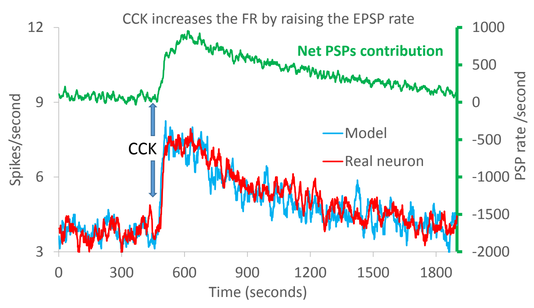
AHP: Several consecutive spikes are needed to get a deep hyperpolarization.

The **HAP** deeply hyperpolarises the cell making it unable to fire. However, its effect only last for 30-50ms.

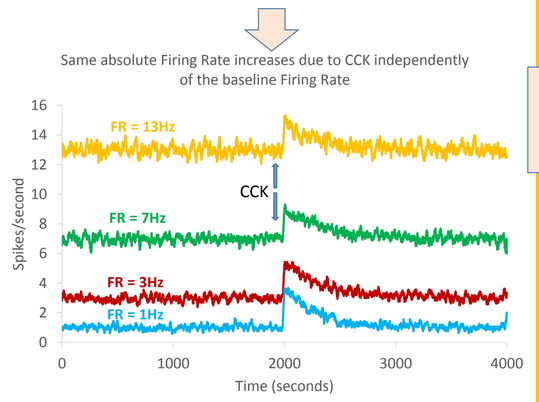
The **AHP** also hyperpolarises the cell, but only the accumulation of many consecutive spikes prevents new firing. However, the effect, when produced, can last for seconds.



The interspike interval distribution shows how often two consecutive spikes have a particular distance between them. These histograms are constructed from the activity shown in the panel below, showing that the model closely matches the precise statistical features of oxytocin neurons.



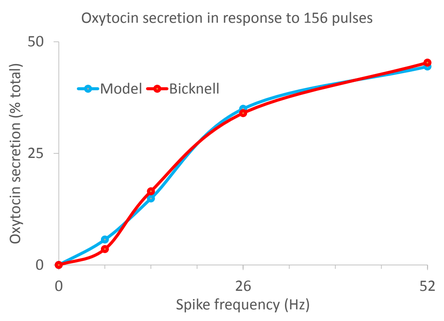
Oxytocin neurons are strongly excited when the gut peptide cholecystokinin (CCK) is injected i.v. , and a typical response from a rat oxytocin cell is shown above in red. With a model cell that has a HAP and an AHP (in blue) it is possible to match this response very closely. In this simulation, CCK increases the EPSP rate, making the net PSPs (EPSPs + IPSPs) clearly positive, as shown in green – the increase in EPSP rate decays exponentially with the known half life of CCK in blood.



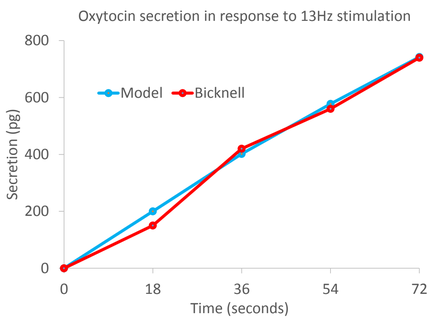
We know from electrophysiological recordings that the response of oxytocin neurons to CCK is independent of the baseline firing rate. The model (above) matches that behavior accurately.

Secretion Model

Oxytocin neurons project axons to the posterior pituitary gland. The spikes produced at the cell bodies propagate down the axons and trigger oxytocin secretion from the terminals. However, oxytocin secretion is a very non-linear function of the spike rate. A given number of spikes produce much more secretion when they occur close together.

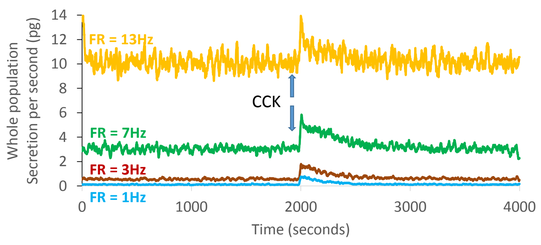


More oxytocin is secreted from the pituitary when a train of 156 pulses is applied at higher frequencies, matching experimental data (from Bicknell 1988) .

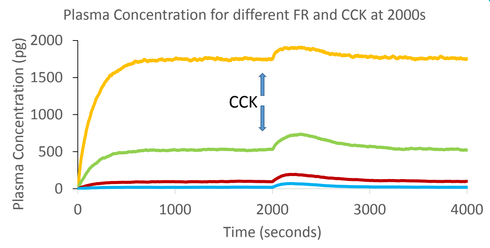


Oxytocin secretion is very steady over time during stimulation at 13Hz (Bicknell et al. 1984). The model is able to match that behavior as well.

Spiking + Secretion Model

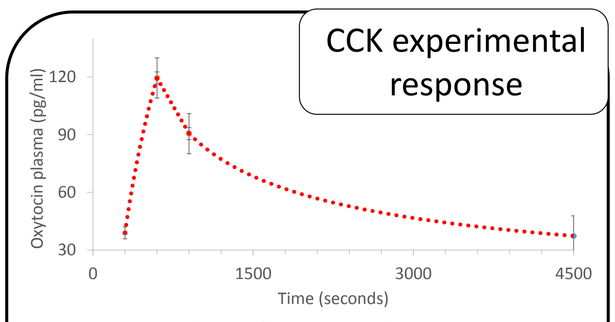


Secretion is a function of spike rate, but it is very non-linear. The model produces more secretion for higher firing rates in both the baseline and after CCK.



Plasma oxytocin concentration reaches a plateau that depends on the firing rate. That plateau is much higher for higher spike frequencies. However, CCK produces a fairly similar increase in plasma concentration regardless of basal firing rate both in the model and in experimental data.

CCK experimental response

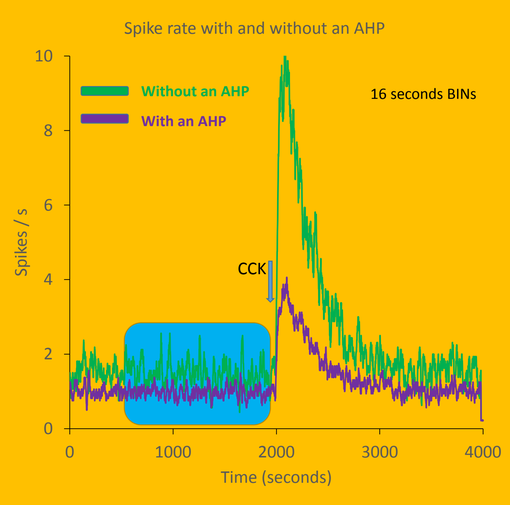


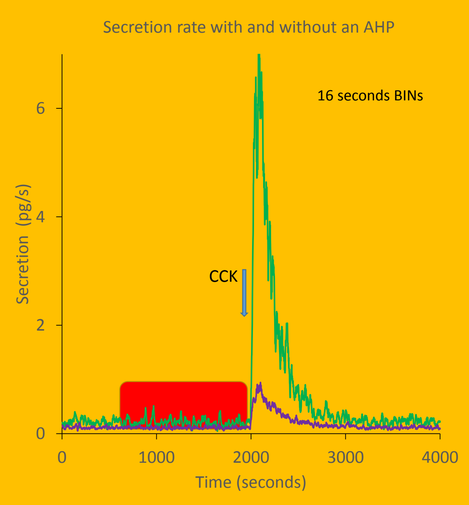
Average oxytocin plasma of 23 rat exposed to CCK. Measurements were taken at the baseline and 300 s, 600 s and 70 minutes after CCK. Trend lines are approximate.

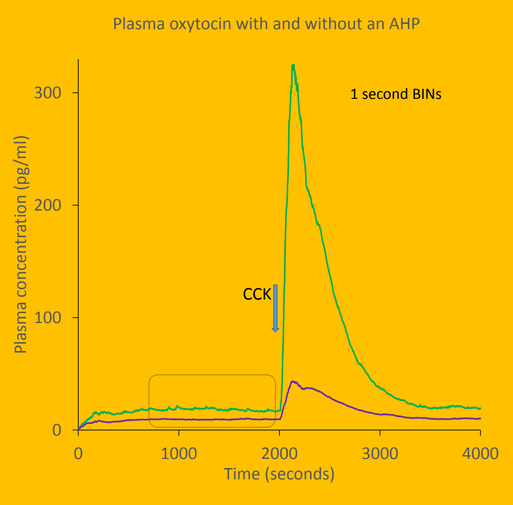
The AHP role

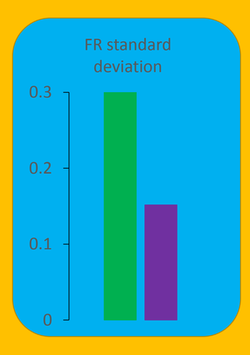
Previously, we showed that the AHP reduces the variability of firing rate of oxytocin neurons. Due to the non-linearity in secretion, we wondered if the AHP was even more important in reducing the variability of oxytocin secretion.

To test this, we compared secretion from a model cell with and without an AHP. We show below how the AHP is affecting the baseline behavior and the response to CCK in the spike rate –left-, secretion –middle- and plasma concentration –right, assuming a half-life of 2 min for secreted oxytocin.



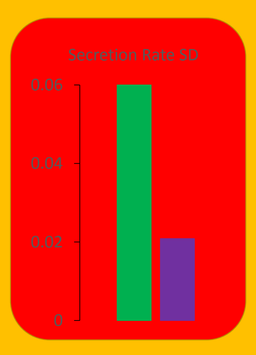






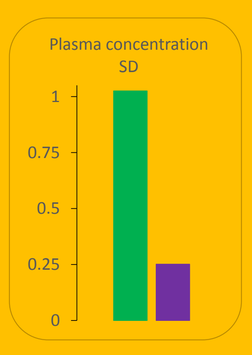
The basal firing rate is less variable with an AHP than without it.

The model was given a PSP rate that produced an average firing rate of 1 spike/s, which increased to 3.5 spikes/s after CCK. Removing the AHP results in a slightly higher basal firing rate but a massively greater response to CCK



The basal secretion rate is much less variable with an AHP than without it.

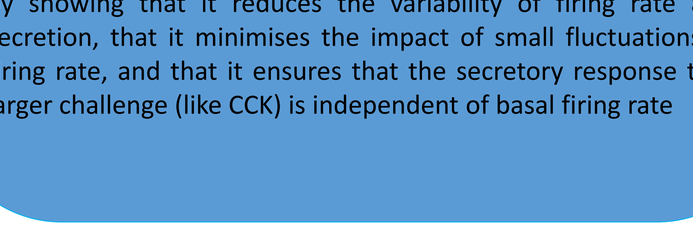
Secretion is a non-linear function of the firing rate. When there is a fast change in firing rate, as produced by CCK, the non-linearity is much larger without the AHP.



The basal oxytocin concentration in plasma is much less variable with an AHP than without it.

Without the AHP, the oxytocin plasma concentration would vary extremely following modest changes in the PSP rate. The AHP minimises these fluctuations.

The model reproduces how plasma oxytocin concentrations change after injection of CCK.



In vivo, oxytocin neurons typically fire at a baseline of 1 spike/s. At that rate, when CCK is injected, the plasma concentration is three times bigger after 300 s and two times after 600 s. Under those restrictions, a FR = 1 spike/s and the presence of the AHP, we can obtain the same results with our model multiplying by 10.000 the modelled spike and secretion activity of a single oxytocin neuron. The advantage is that we do not need to look into the cell membrane potential looking for its FR because we now can obtain that information from computational parameter values.

Spiking + Secretion Model

its ability to make predictions and the AHP importance

From this model, we can infer the spiking behaviour of oxytocin neurons measurements of plasma oxytocin alone.
We have also revealed the physiological importance of the AHP – by showing that it reduces the variability of firing rate and secretion, that it minimises the impact of small fluctuations in firing rate, and that it ensures that the secretory response to a larger challenge (like CCK) is independent of basal firing rate

References

Bicknell RJ (1988). Optimizing release from peptide hormone secretory nerve terminals. *J Exp Biol* 139: 51–65.
Bicknell, R J, D Brown, C Chapman, P D Hancock, and G Leng (1984). 'Reversible fatigue of stimulus-secretion coupling in the rat neurohypophysis.' *J Physiology* 348: 601–13.
MacGregor, D J., and G Leng (2013). 'Spike triggered hormone secretion in vasopressin cells; a model investigation of mechanism and heterogeneous population function'. *PLoS Comput Biol* 9, no.: e1003187.
Maícas Royo, J, C H. Brown, G Leng, and D J MacGregor (2015). 'Oxytocin neurones: intrinsic mechanisms governing the regularity of spiking activity'. *J Neuroendocr*, n/a – n/a. doi:10.1111/jne.12358.

This work was supported by Nudge-it (http://www.nudge-it.eu/) a research program that aims to better understand decision-making in food choice and to build predictive models to contribute to improving public health policy. Nudge-it is a European Commission-funded FP7 project.