Computational model of a single oxytocin neuron.

Spiking, secretion and plasma oxytocin dynamics.

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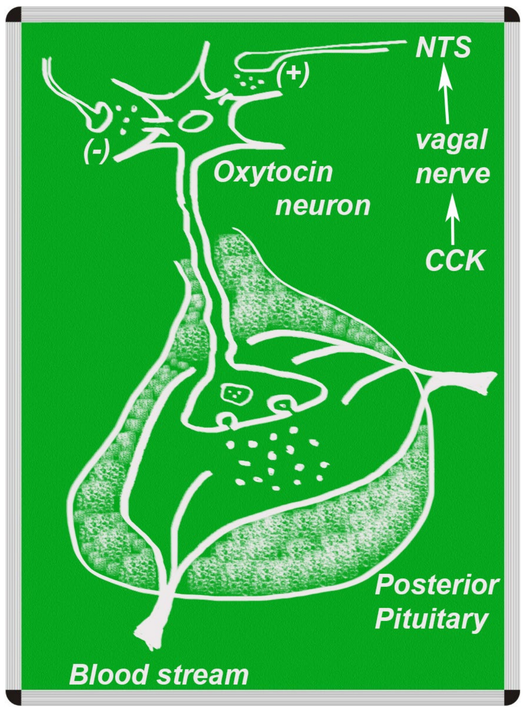
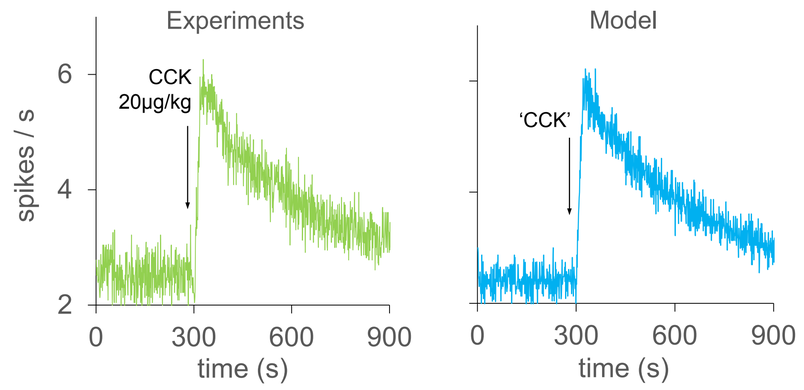
About 9000 magnocellular oxytocin neurones are located in the rat hypothalamus. They project their axons to the posterior pituitary where they secrete oxytocin into the bloodstream



SPIKING MODEL

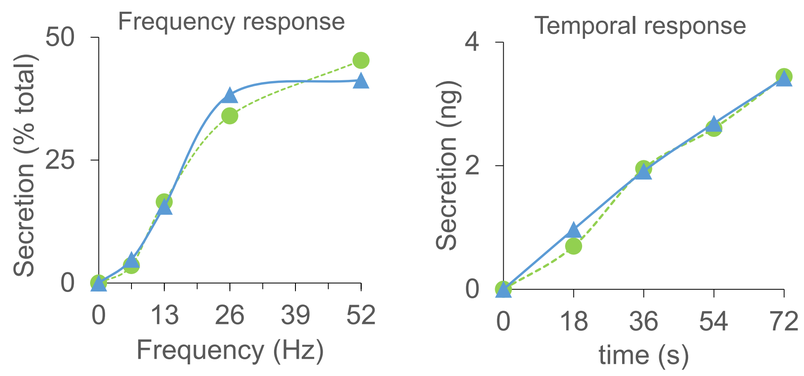
mimics electrophysiological data of oxytocin cells responding to cholecystokinin (CCK), a peptide produced in the gut after food intake.



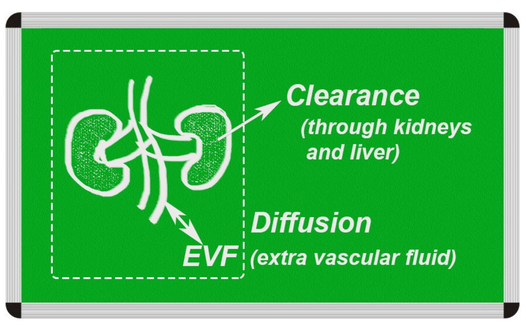
Responses of oxytocin neurons of the supraoptic nucleus to i.v. CCK, *in vivo* and in the model. **Left)** Average response of 23 oxytocin neurons. **Right)** Response of a model oxytocin cell to CCK, simulated as an increase in postsynaptic potentials (PSP) that decays exponentially with a half-life of 230 s. The simulation was run 23 times with different random seeds, and the figure shows the average.

SECRETION MODEL

mimics the non-linearity between secretion and spiking activity.

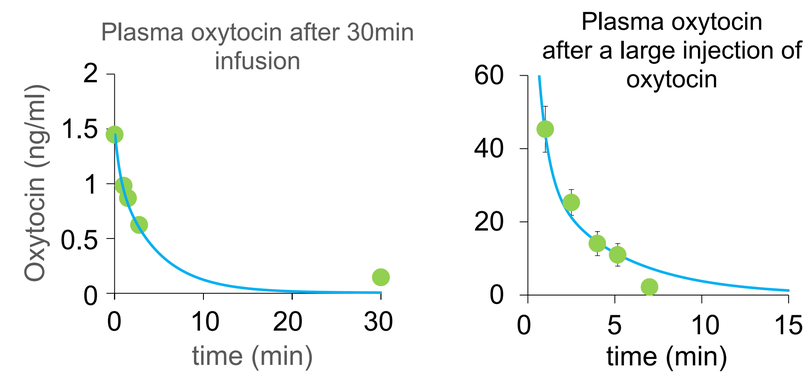


Left) Frequency facilitation. When posterior pituitaries were electrically stimulated at 6.5, 13, 26 and 52 Hz, secretion per pulse was bigger at higher frequencies (green dots and dotted line) (1). The model (blue triangles and line), adapted from a vasopressin secretion model (2), matches that non-linearity. **Right)** Oxytocin neurons can maintain the same secretion for long periods up to a frequency of 13 Hz (3).



DIFFUSION MODEL

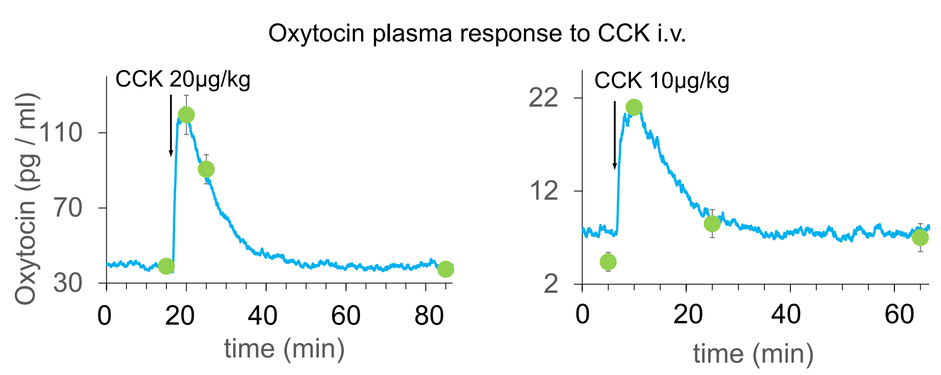
mimics the plasma clearance of oxytocin, replicating the dynamics found after infusion and injection of oxytocin.



Two-compartment diffusion model showing oxytocin plasma response to CCK. Green dots show oxytocin measurements in rats (4, 5). Blue lines are results obtained with our model following the same protocols. **Left)** After 30 min oxytocin infusion of 3ng/100g/min (4) **Right)** After oxytocin injection of 440ng/100g (5).

Spiking model → Secretion model → Diffusion model

Combining the spiking, secretion and diffusion models, we can infer the spiking activity that produces a given plasma oxytocin concentration. These inferences match spiking data recorded during infusions of NaCl that linearly increase plasma osmotic pressure, or i.v. injection of CCK.



With the combined model, we can match the CCK-plasma oxytocin response (green points ±SEM) for two experimental data sets by only changing the EPSP rate at baseline. **Left)** Plasma oxytocin (green dots) from 23 conscious virgin rats given CCK. The rest of the parameters are the same as the ones obtained to match the average spiking. **Right)** 5-10 rats with a 10ug/kg CCK i.v.

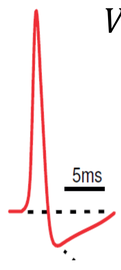
Spiking model → Secretion model → Diffusion model

Every oxytocin neuron receives hundreds of input signals that produce postsynaptic potentials (PSPs). Excitatory PSPs depolarize its membrane potential (*Vm*), and inhibitory PSPs hyperpolarize 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 *Vm* reaches *Vthreshold*, a spike is produced and the neurone produces a **HAP** (hyperpolarising afterpotential) and an **AHP** (after-hyperpolarisation) (6)**.**

*The **AHP** acts as a filter, protecting the final product of oxytocin cells from noisy fluctuations.*

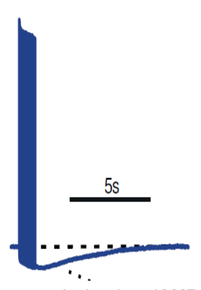
$$V_m = V_{rest} + V_{syn} - HAP - AHP$$



hyperpolarising after potential (**HAP**)

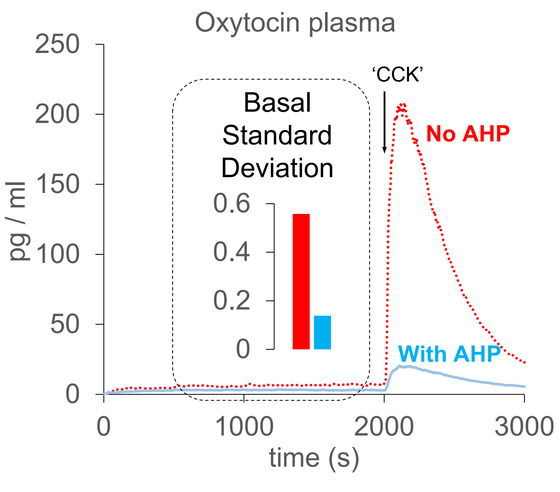
The **HAP** has a large magnitude (~10mV) but only lasts for 30-50ms.

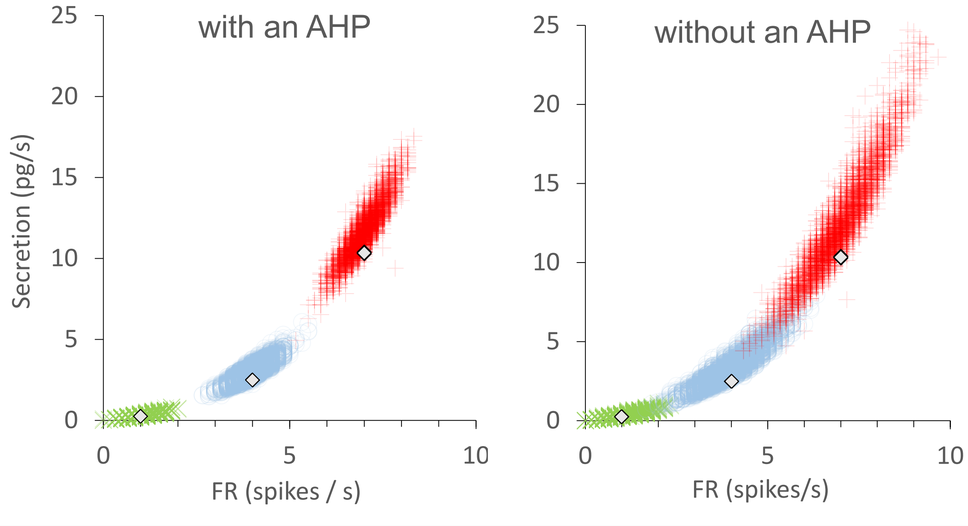
The **AHP** is smaller but longer lasting, accumulating over consecutive spikes to slow firing.



slow after-hyperpolarization (**AHP**)

The presence of an AHP in oxytocin neurons dramatically reduces the variability of their spiking activity but also that of oxytocin secretion and plasma levels, at the baseline and in response to CCK.





Role of AHP combined with the frequency facilitation in secretion. Large diamonds represent the secretion response to mean firing rates of 1, 4 and 7 spikes/s. Dot clouds represent the secretion response during 1200s when the modelled neuron receives random PSPs that produce average firing rates of 1 (green crosses), 4 (blue circles) and 7 spikes/s (red pluses).

References

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