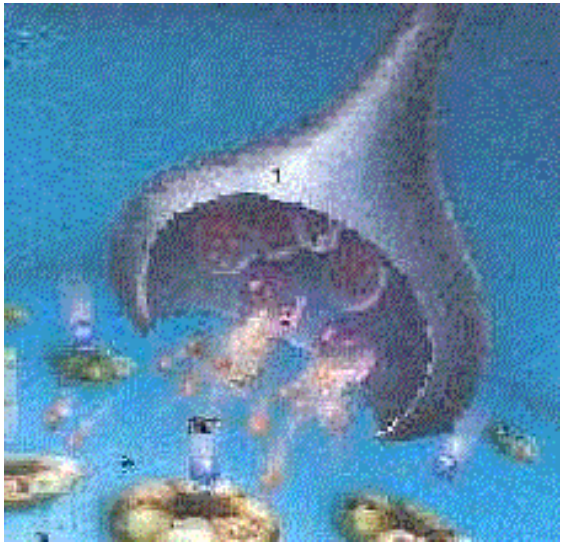
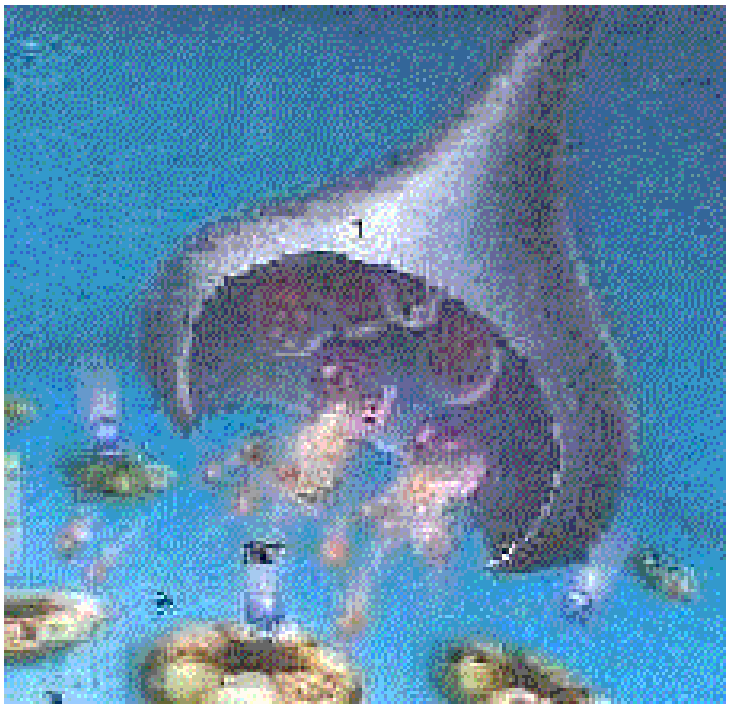
Modelling the model systems

Gareth Leng



THE UNIVERSITY OF EDINBURGH

Once upon a time, neurons were thought to communicate by transmitters that excited or inhibited other neurons.

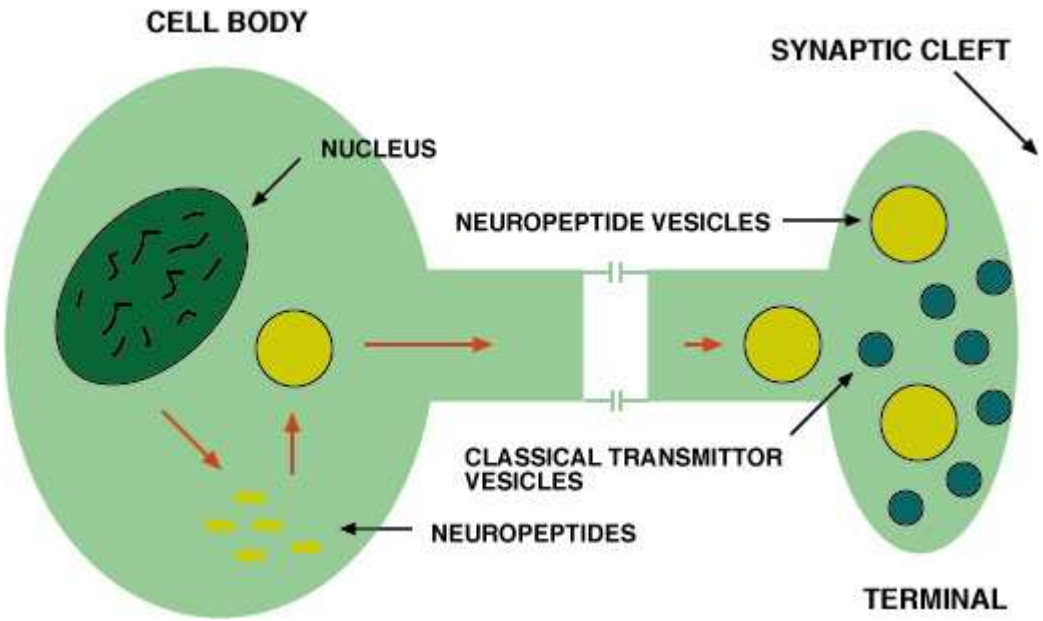


These signals were regulated by action potentials that evoked transmitter release at synapses, with short lasting effects.

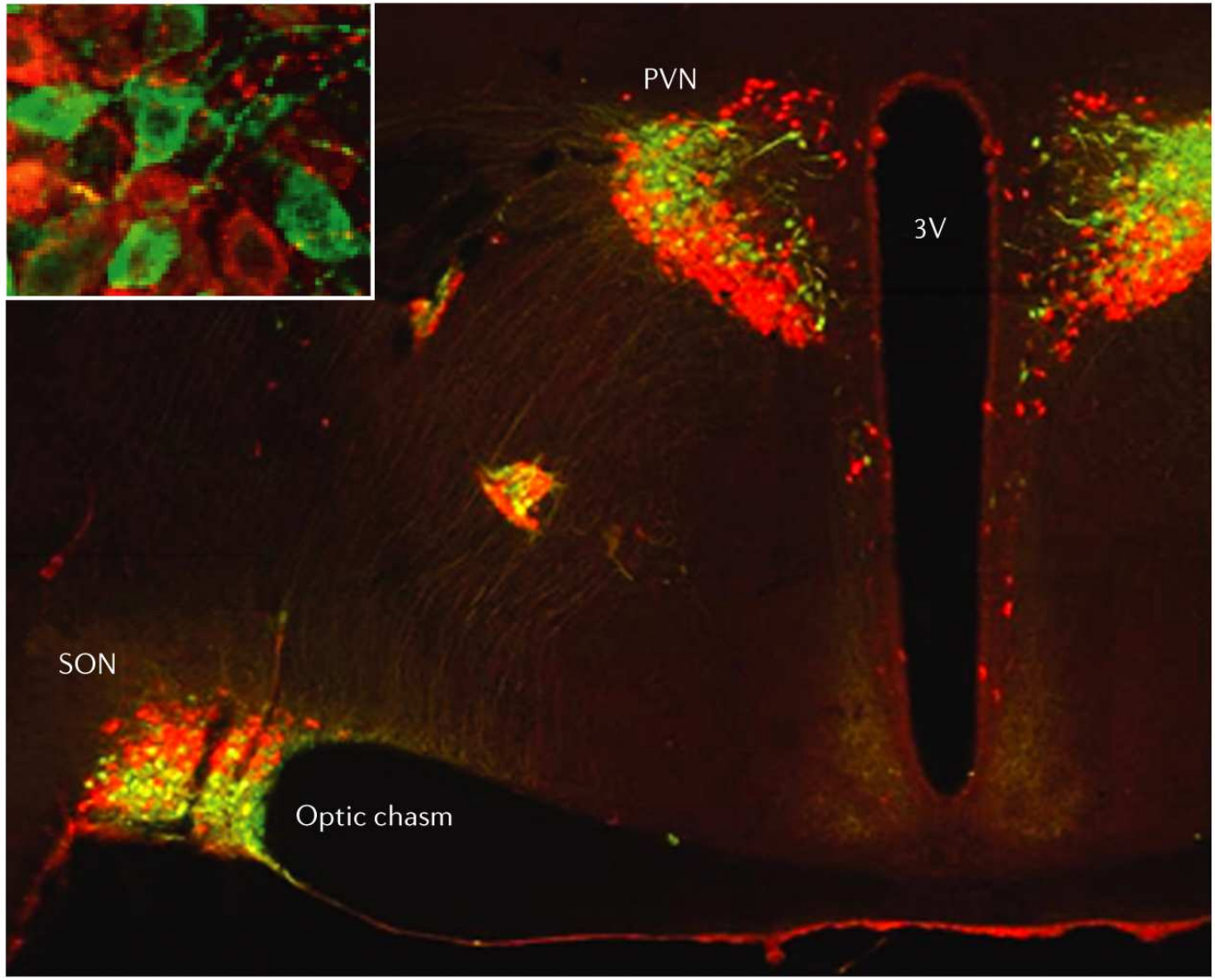
Information processing consisted of sophisticated spatio-temporal patterns of activation.

GABA, glutamate, ACh and the catecholamines

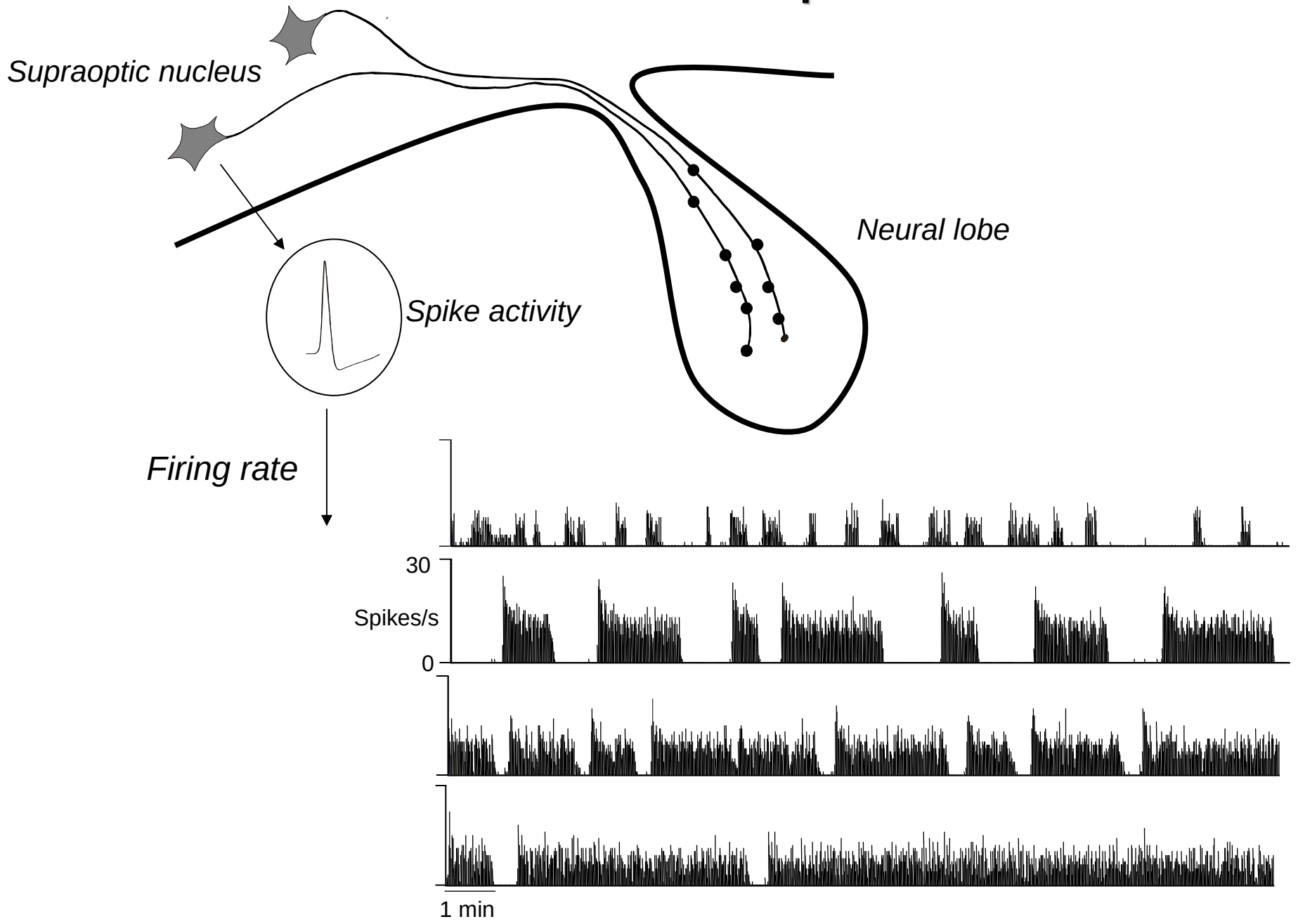
Peptides in the brain…..



Oxytocin, vasopressin, cholecystokinin, opioids, tachykinins, GHRH, LHRH, TRH, CRF, somatostatin, NPY, orexins, substance P, apelin, CART, AgRP, PACAP, galanin, VIP, urocortin, PrRP, neurotensin, neuromedins, ANP, BNP, angiotensin, BDNF, ghrelin, MCH, a-MSH…. >100 so far

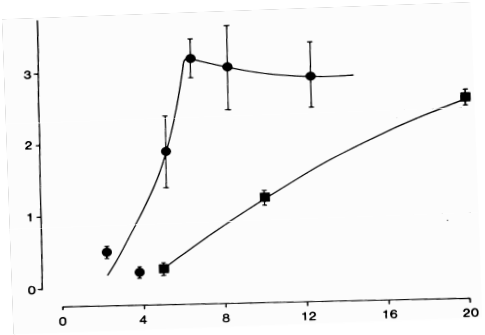


Vasopressin Cells

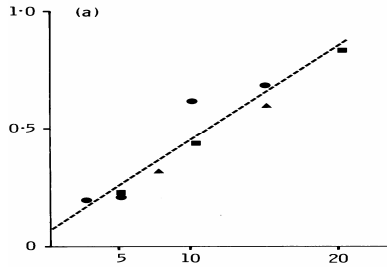


Phasic firing is *efficient* for vasopressin secretion

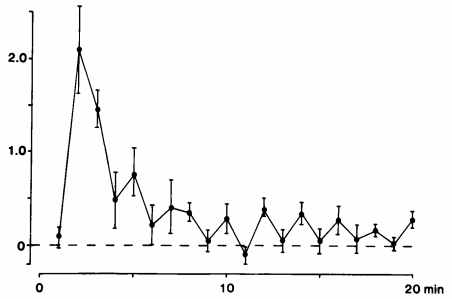
Secretion maximal at ~13 Hz (Dutton & Dyball 1977)

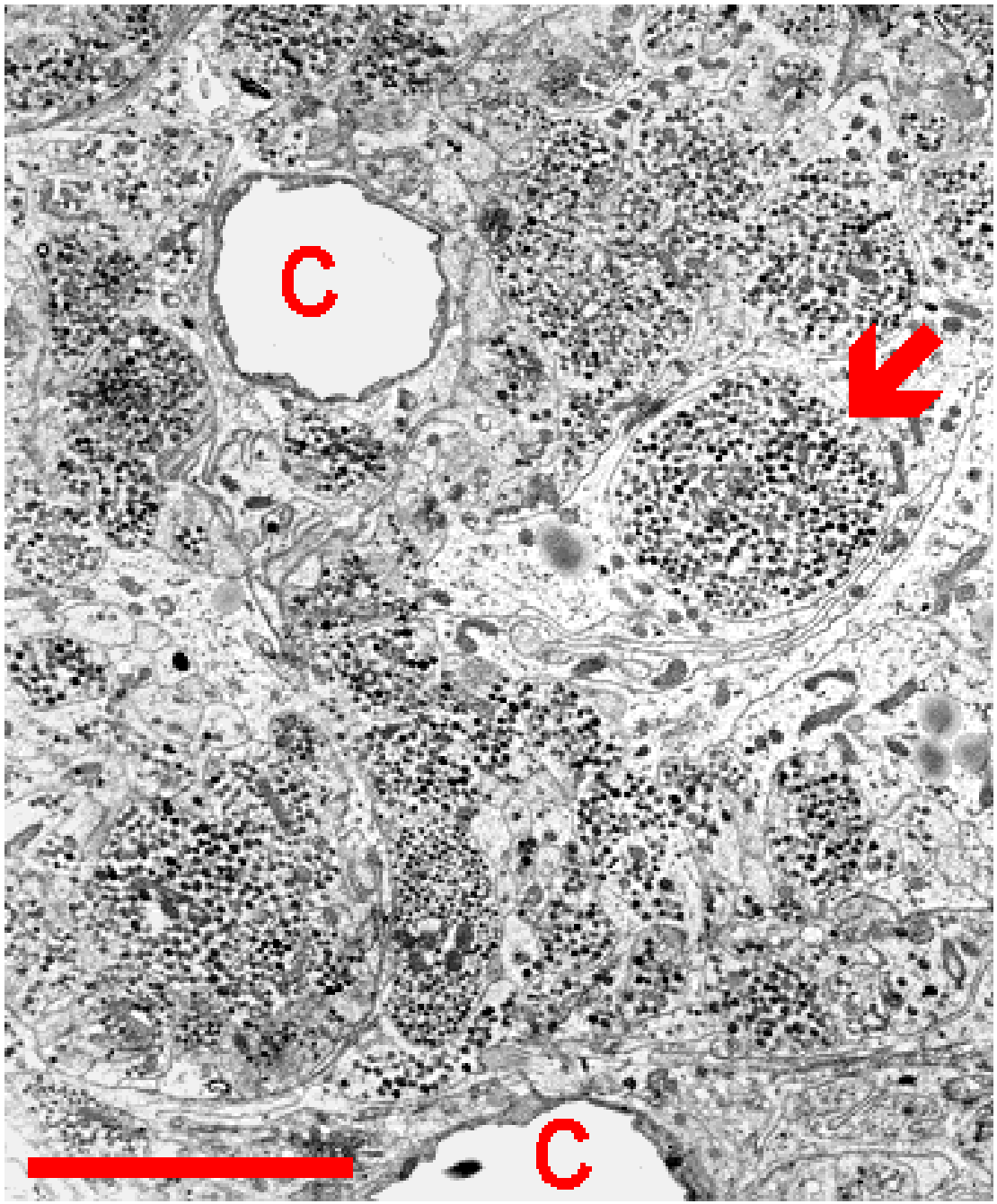


… increases with burst duration up to ~20 s (Shaw *et al.* 1984)



… fatigues at longer burst durations, reversed by silences Bicknell *et al.* (1984)



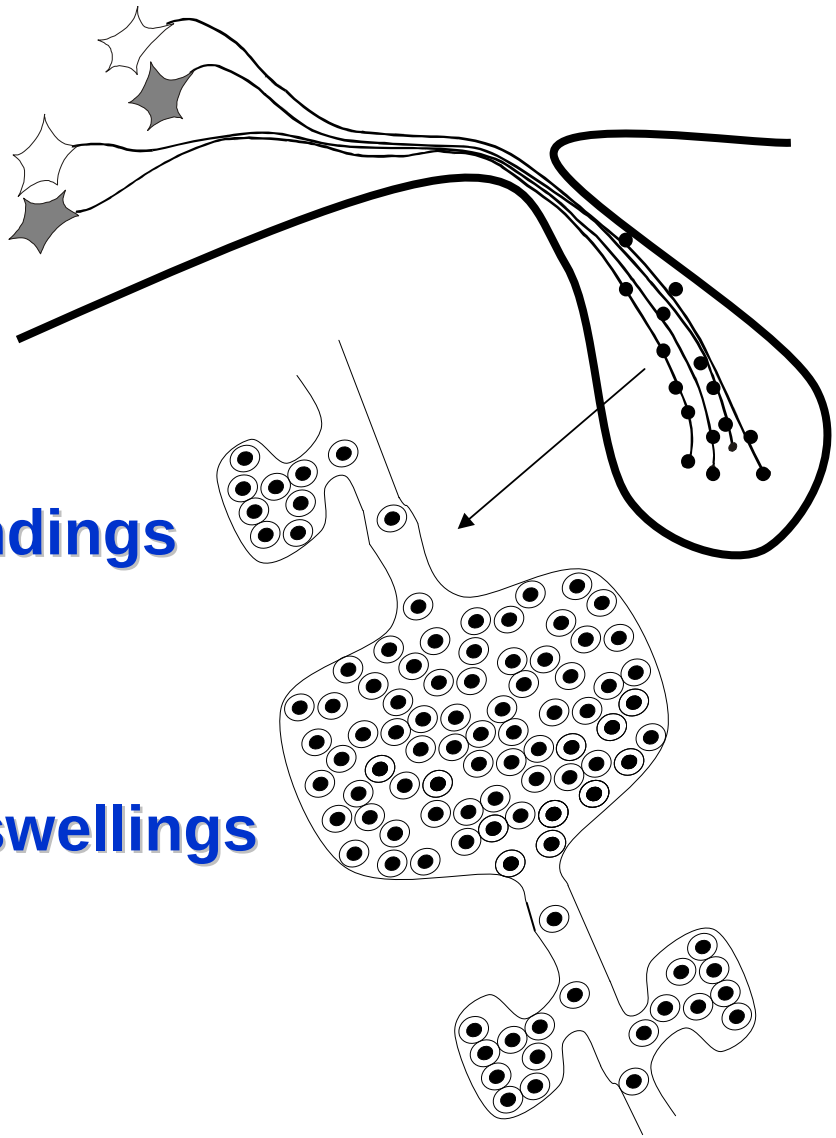


In the neural lobe…

9,000 oxytocin cells
and
9000 vasopressin cells
project there.

9,000 vasopressin cells

Jean Nordmann (1976)
John Morris (1976)

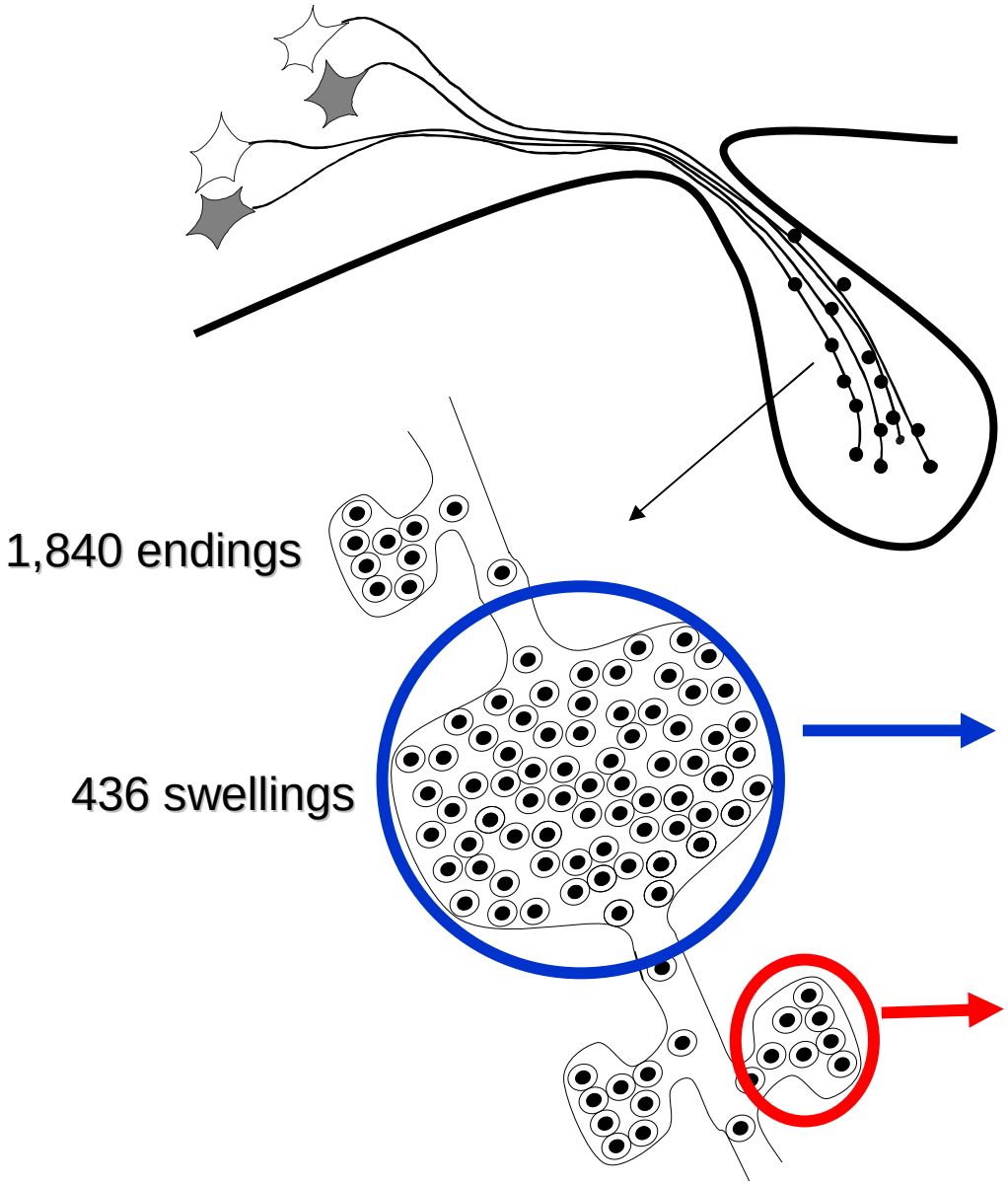


1,840 endings

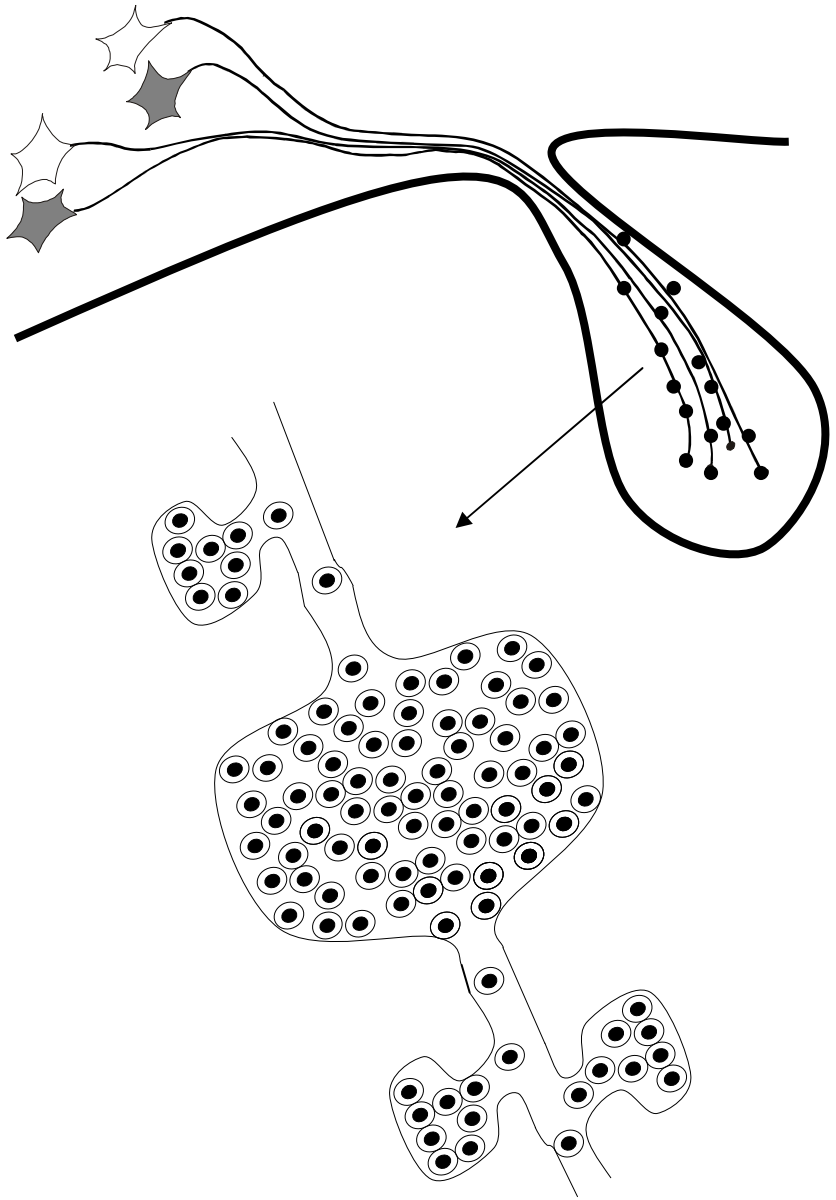
436 swellings

9,000 vasopressin cells

Jean Nordmann (1976)
John Morris (1976)



1.48×10^{10} vesicles



Jean Nordmann (1976)
John Morris (1976)

1.48×10^{10} vesicles

Each vesicle contains 85,000 molecules of vasopressin

How much vasopressin is released per second?

Plasma vasopressin concentration (pg/ml)

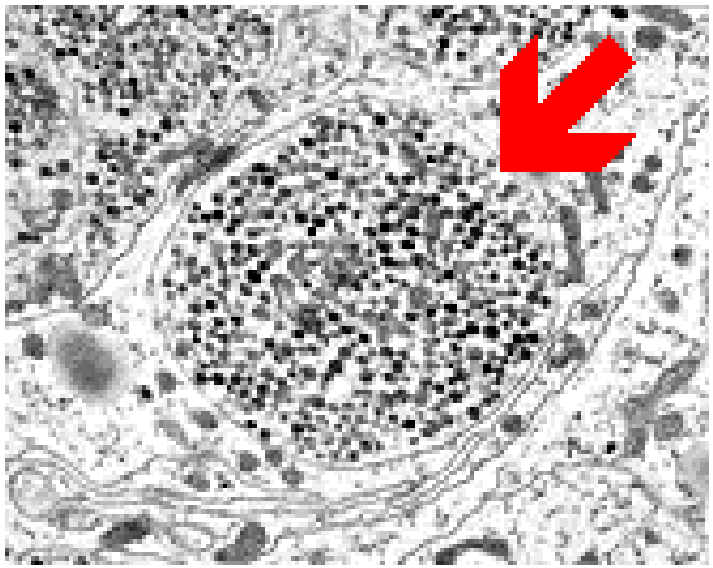
basal conscious	1
dehydrated, conscious	10
basal anaesthesia	85
max stimulated	220

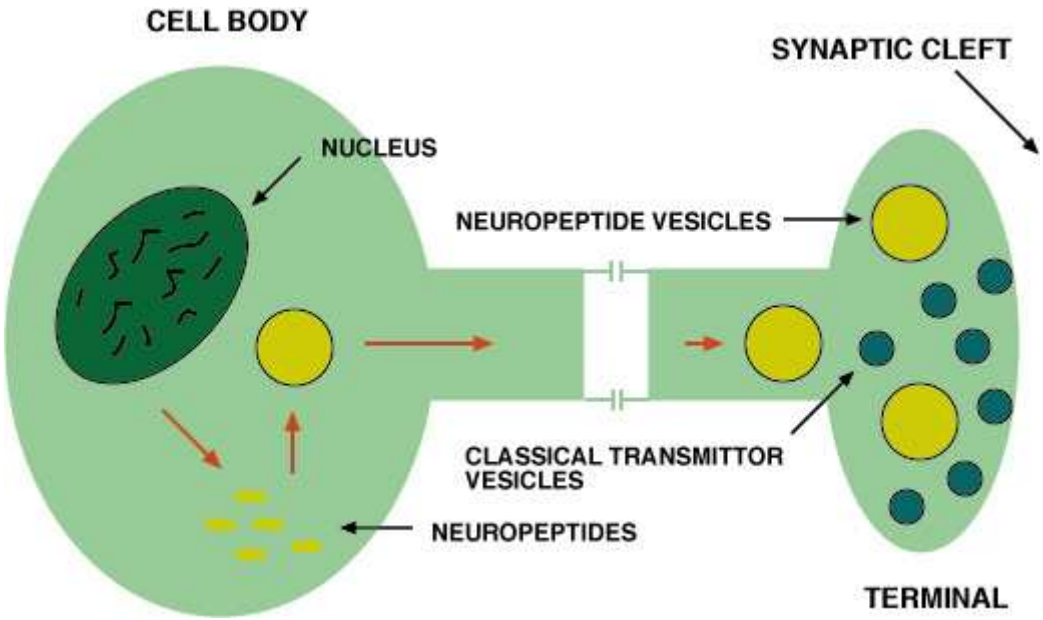
Total in circulation at basal levels (in 60 ml) = **60 pg.**
Half-life ~**2 min.**
Needs secretion rate of **0.35 pg/s**
Daily basal secretion is ~ **30 ng**
(content is enough for ~ 6 days of modest dehydration)

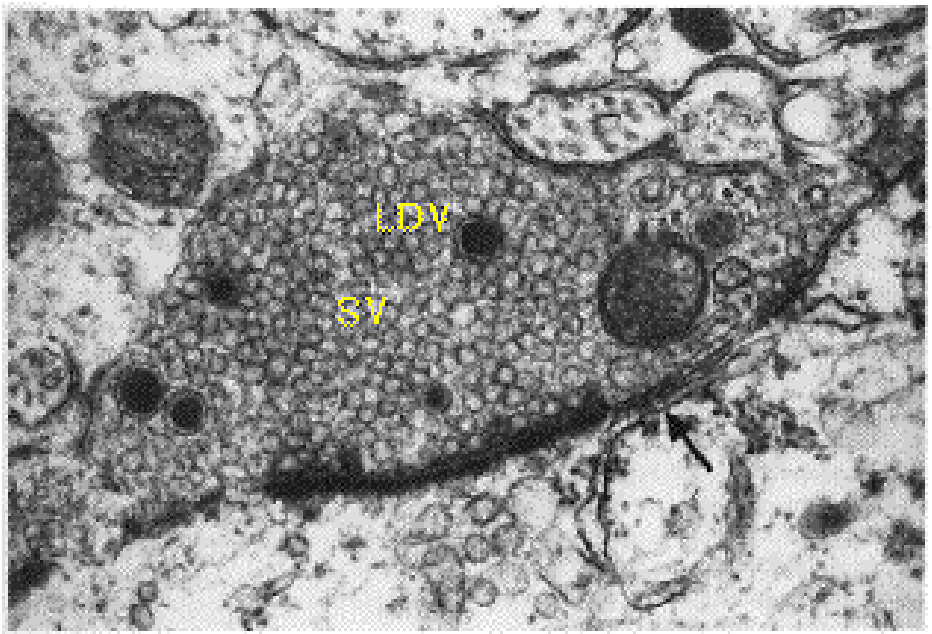
How many vesicles per spike?

basal anaesthesia	**23 vesicles/cell/s**
4 spikes/s	**~5 vesicles/cell/spike**
max stimulated	**58 vesicles/cell/s**
10 spikes/s	**6 vesicles/cell/spike**

2000 release sites
so at any one site it takes
about 400 spikes to release
one vesicle, on average

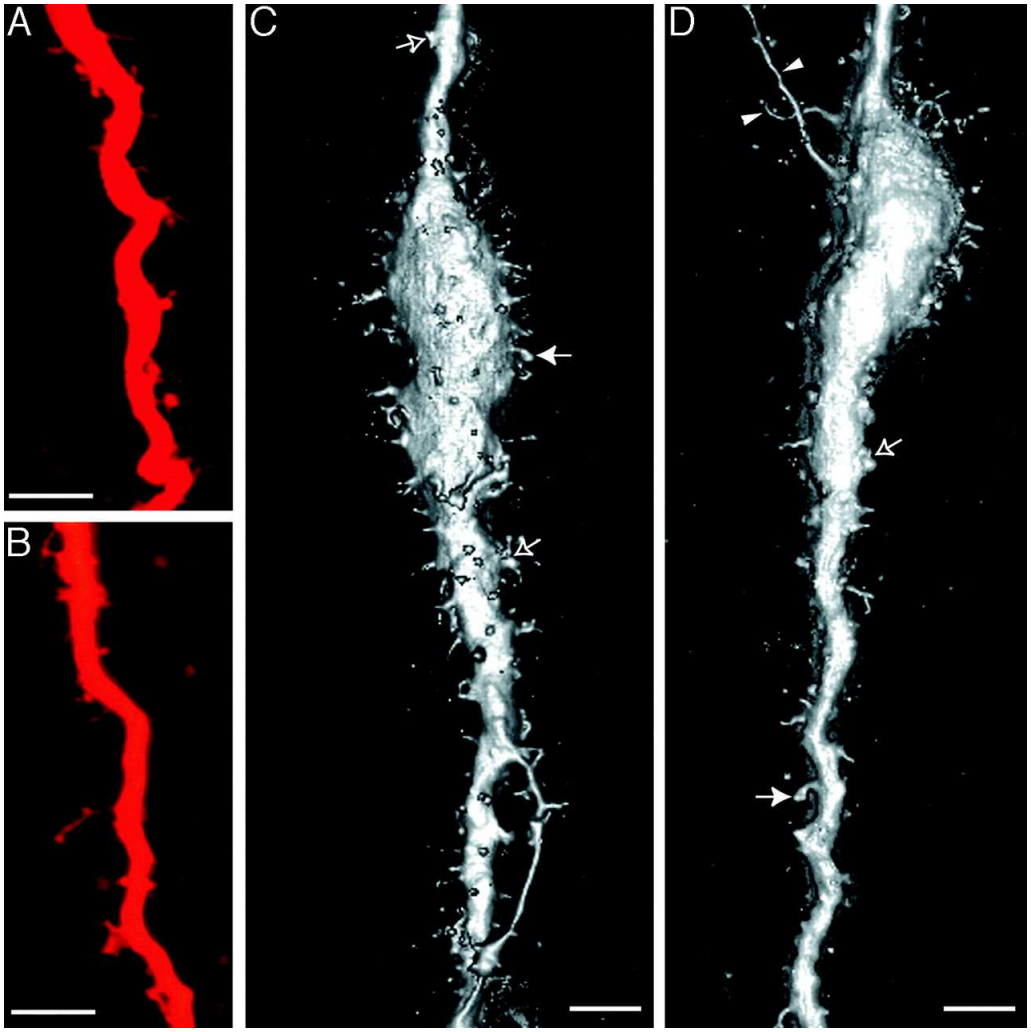






- Peptide vesicles are found in synapses….
- But not many

Confocal images of dendrites of GnRH neurons

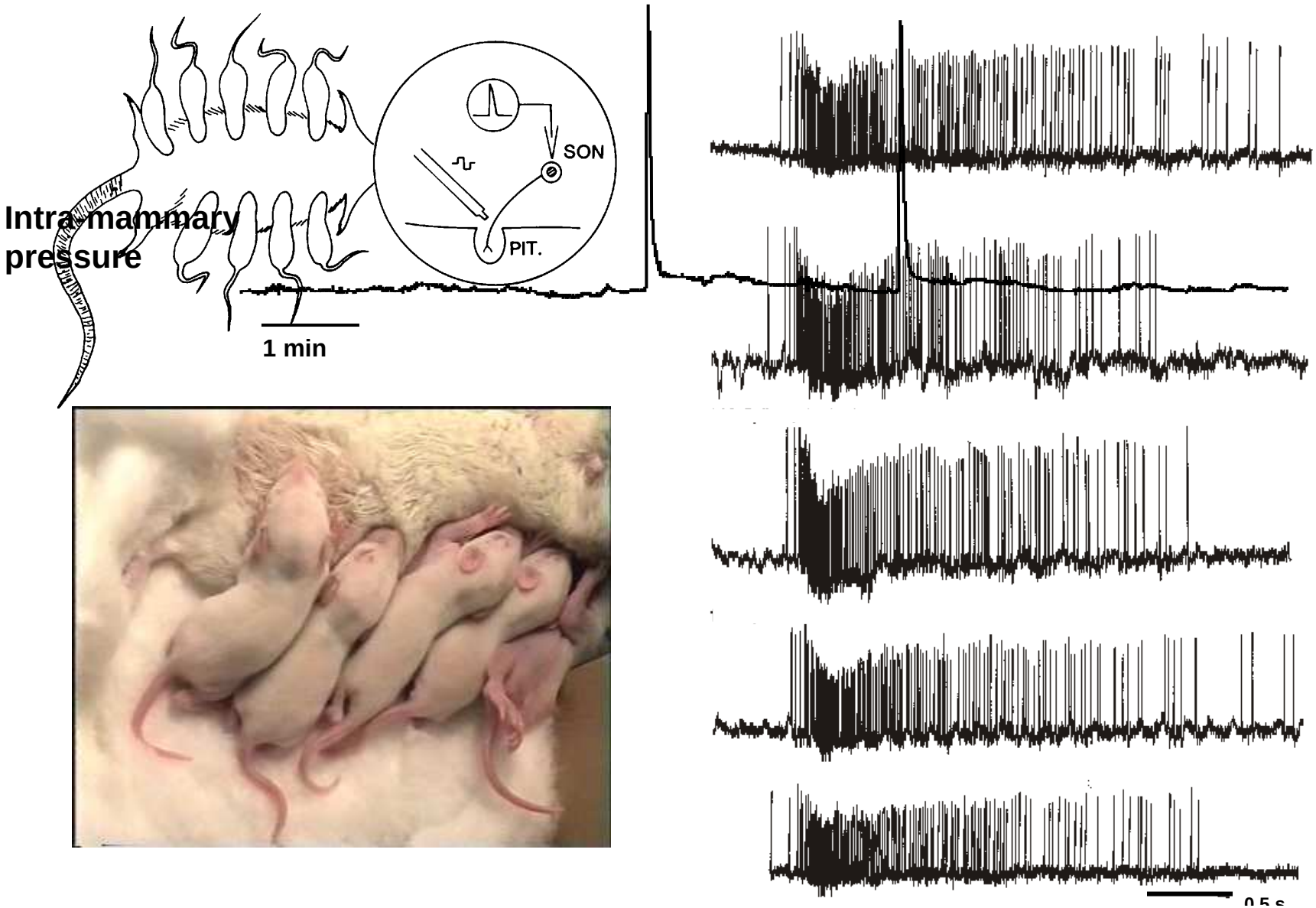


Most peptide is in dendrites.

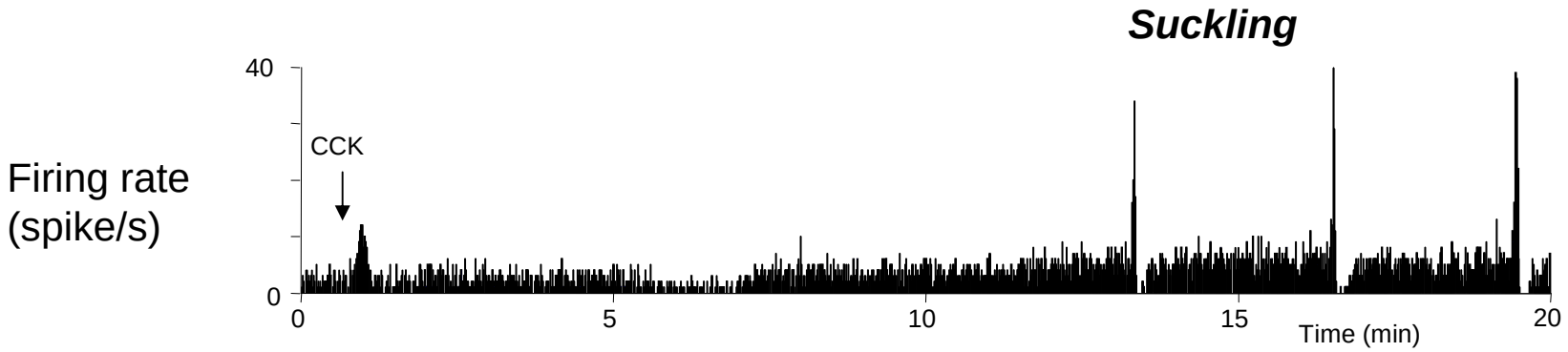
Dendrites are >85% of the cell volume

Campbell, R. E. et al. Endocrinology 2005;146:1163-1169

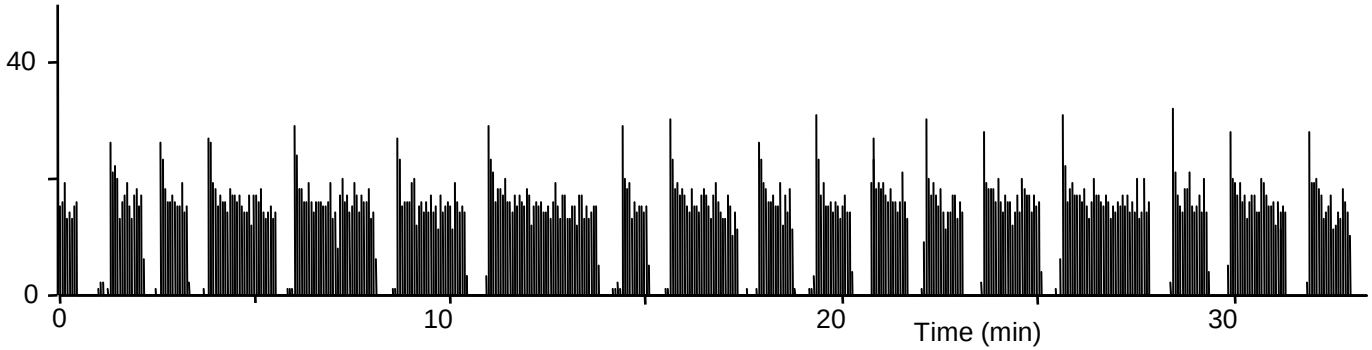
Intermittent, stereotyped bursts



Oxytocin cells

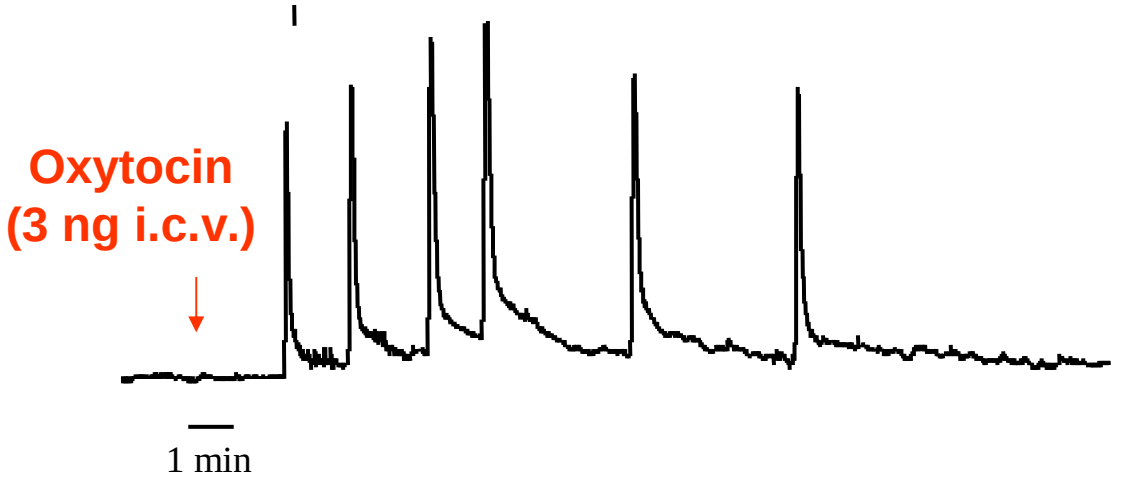


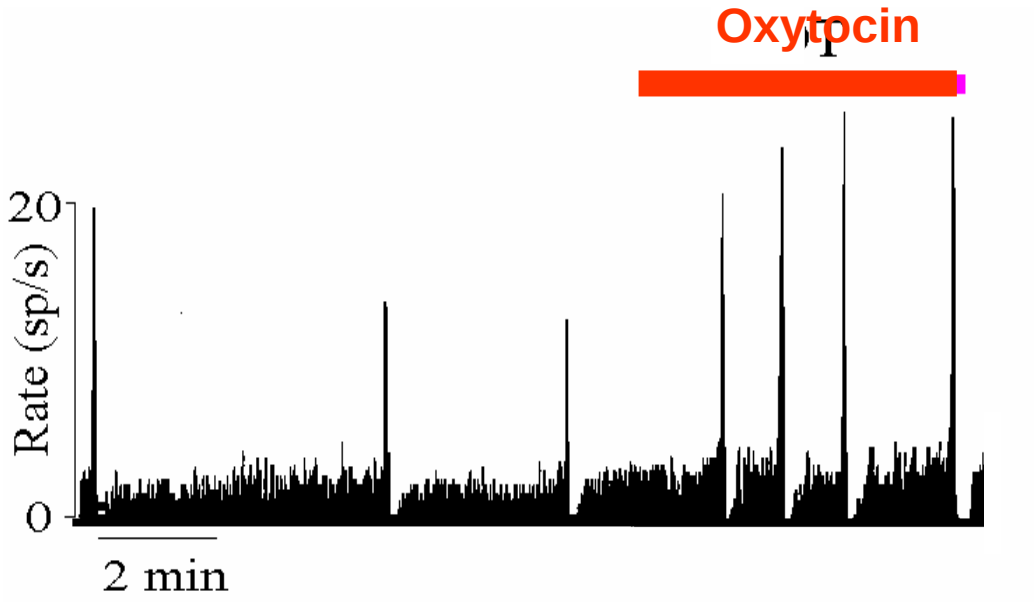
Vasopressin cells



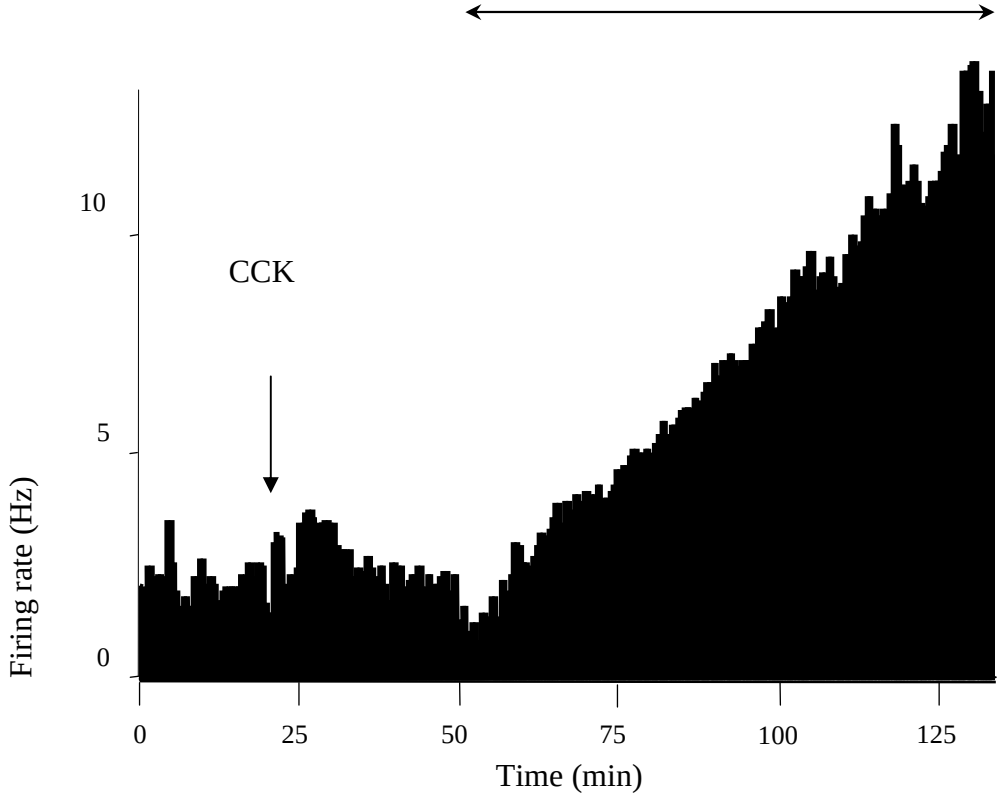
Oxytocin facilitates reflex milk-ejection

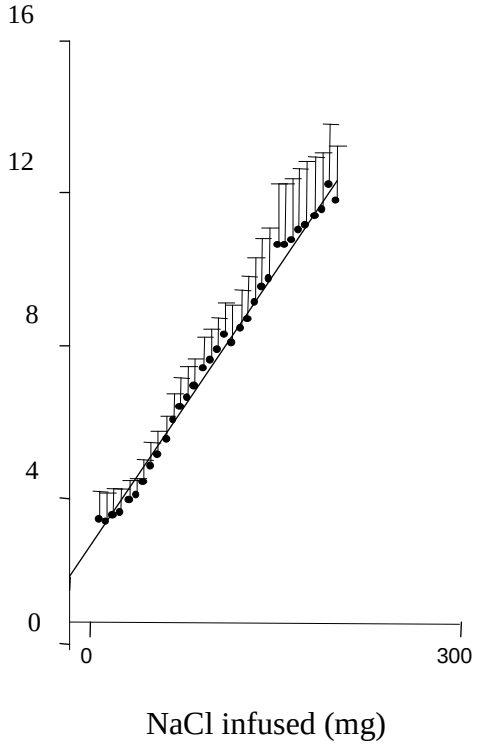
- Oxytocin itself facilitates bursting
- Apparently a positive-feedback system
- *But why does only suckling evoke bursts ?– other ways of activating the cells don't do this*





Hypertonic saline infusions raise the firing rate of oxytocin neurones linearly





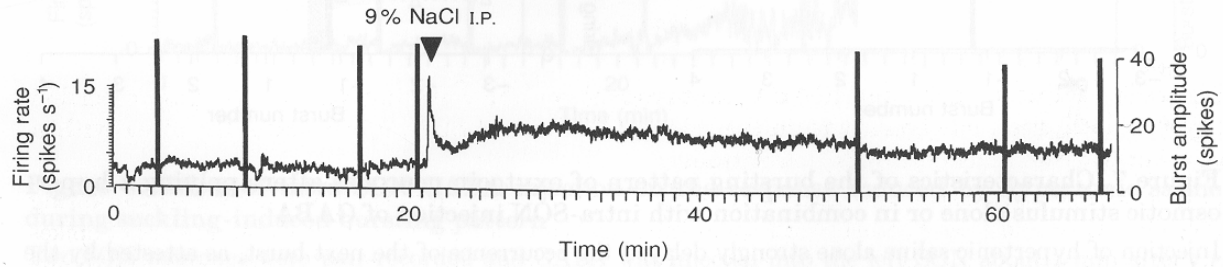
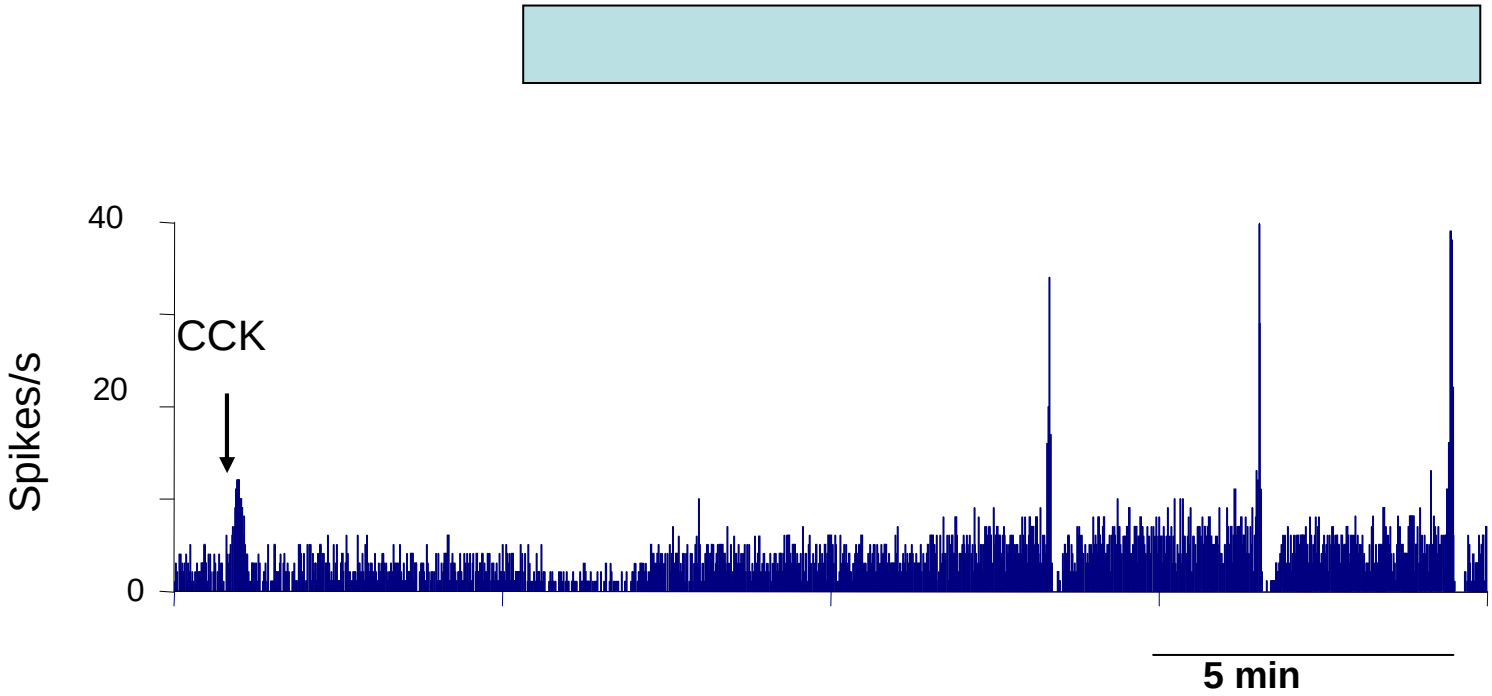


Figure 6. Effect of hyperosmotic stimulus on the bursting pattern of oxytocin neurones during suckling

The bursting looks as though it might result from positive-feedback – but increasing the mean activity of oxytocin cells paradoxically reduces bursting activity

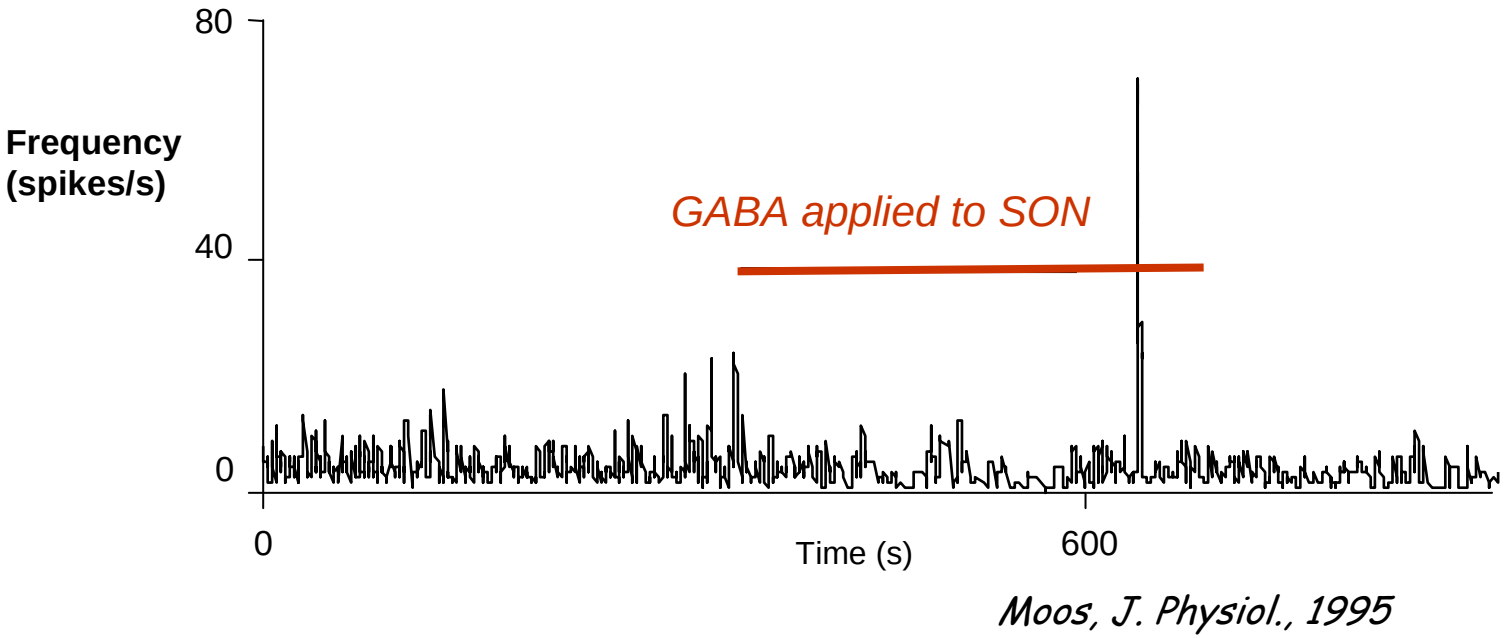
Suckling



Suckling has small, mixed effects on background activity, it tends to inhibit active cells and activate silent cells. Bursts occur every 3-10 min and are approximately synchronised amongst all oxytocin cells.

There is no synchrony in the background activity, but near bursts there is a weak cross-correlation between some pairs of cells, and increased irregularity of firing

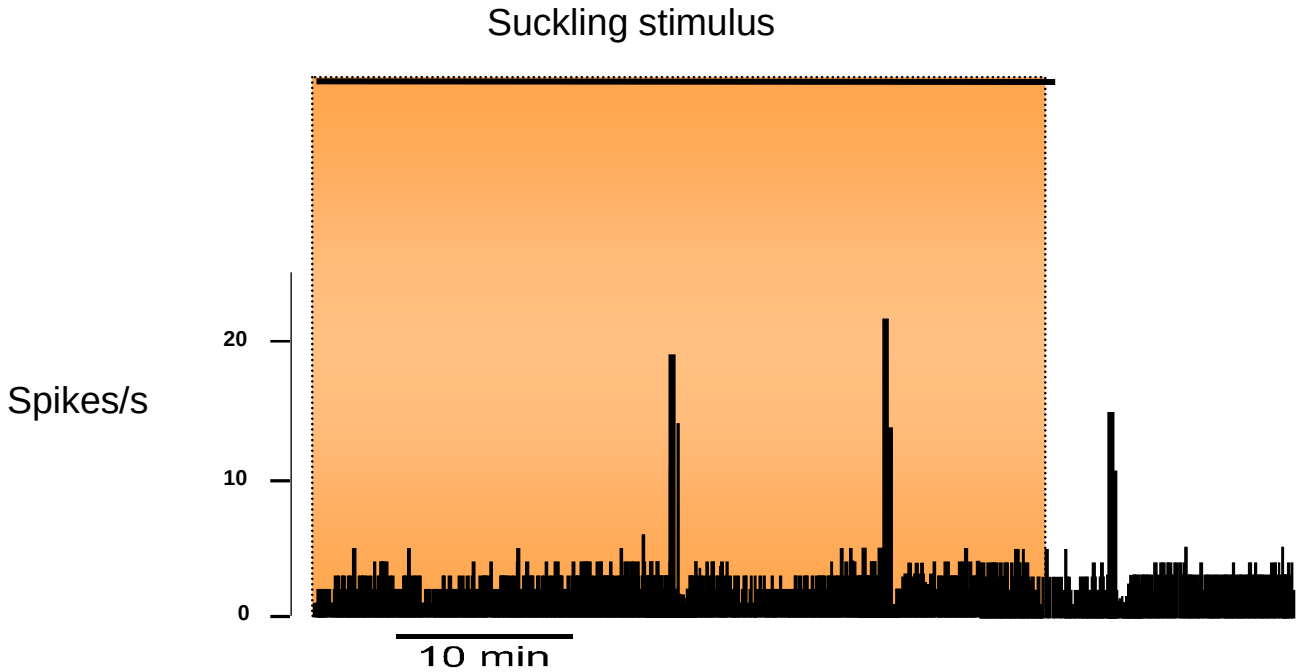
Confusingly, directly inhibiting oxytocin cells can trigger bursts *(only happens during suckling)*



Moos, J. Physiol., 1995

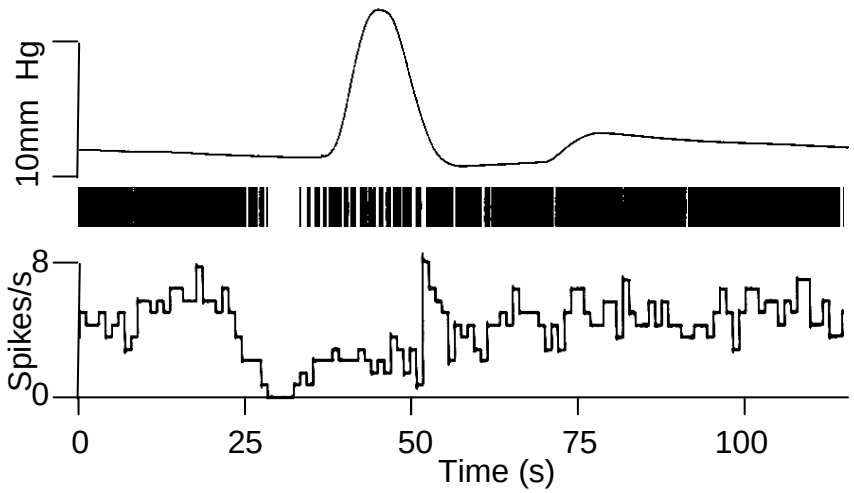
Suckling is necessary for bursting….

Irritatingly, sometimes a single burst will occur *after the suckling stimulus has been removed*



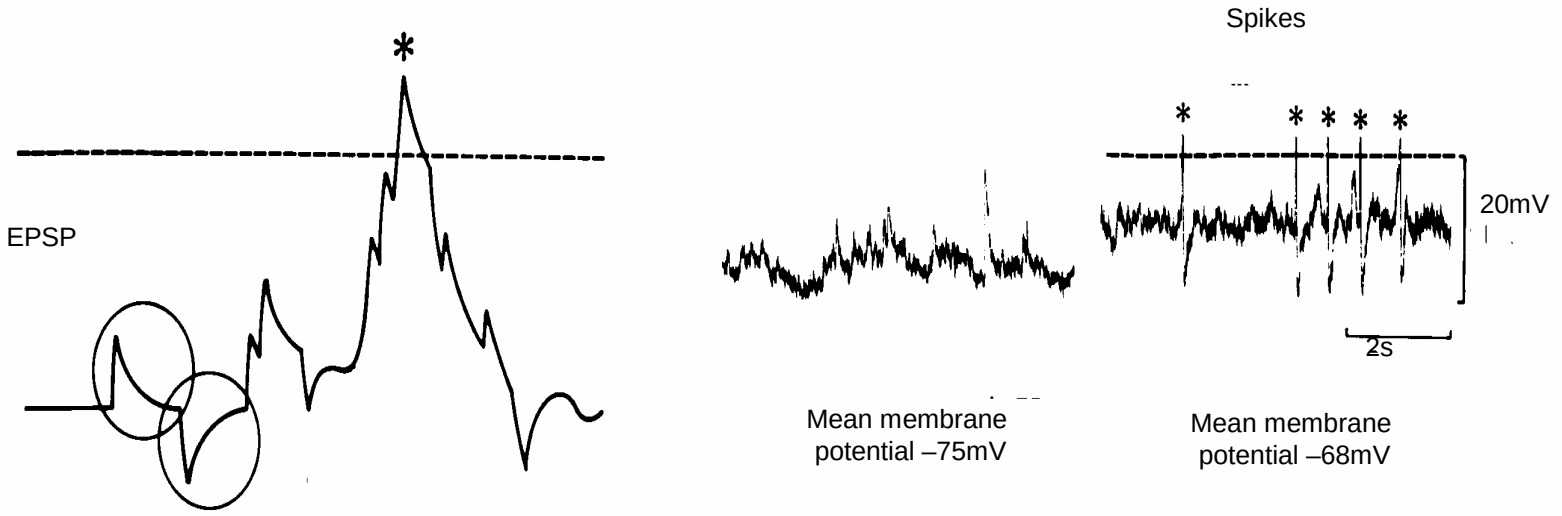
Strangely, although most oxytocin cells burst then fall silent, *some fall silent without bursting*

In vivo

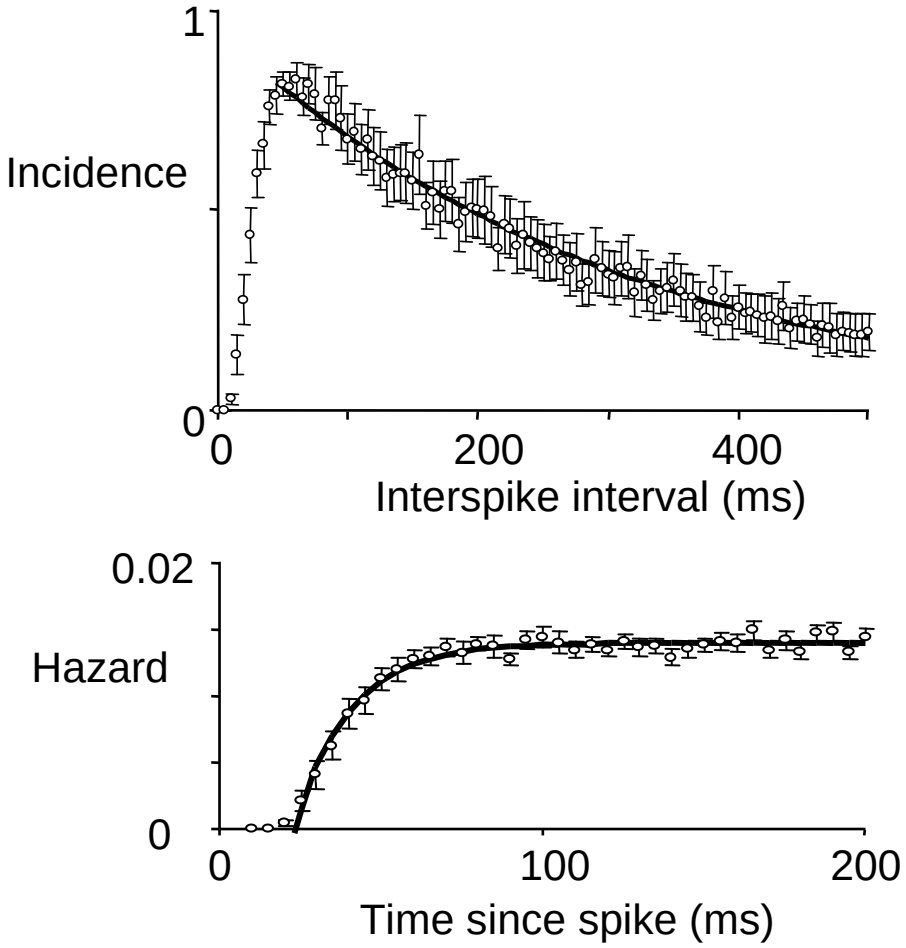


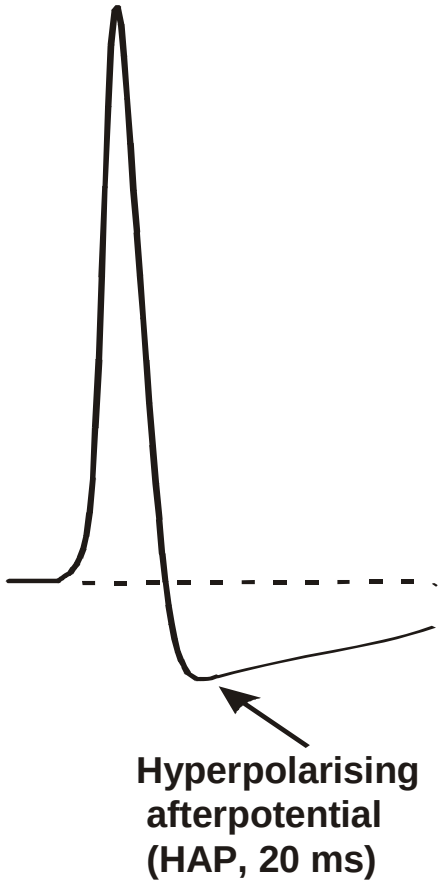
The spike-response model

- EPSP and IPSPs are represented as exponentially decaying pulses
- These are generated randomly
- When the simulated membrane potential crosses a “spike threshold” a spike is generated.
- After each spike, the cell is transiently hyperpolarised /depolarised

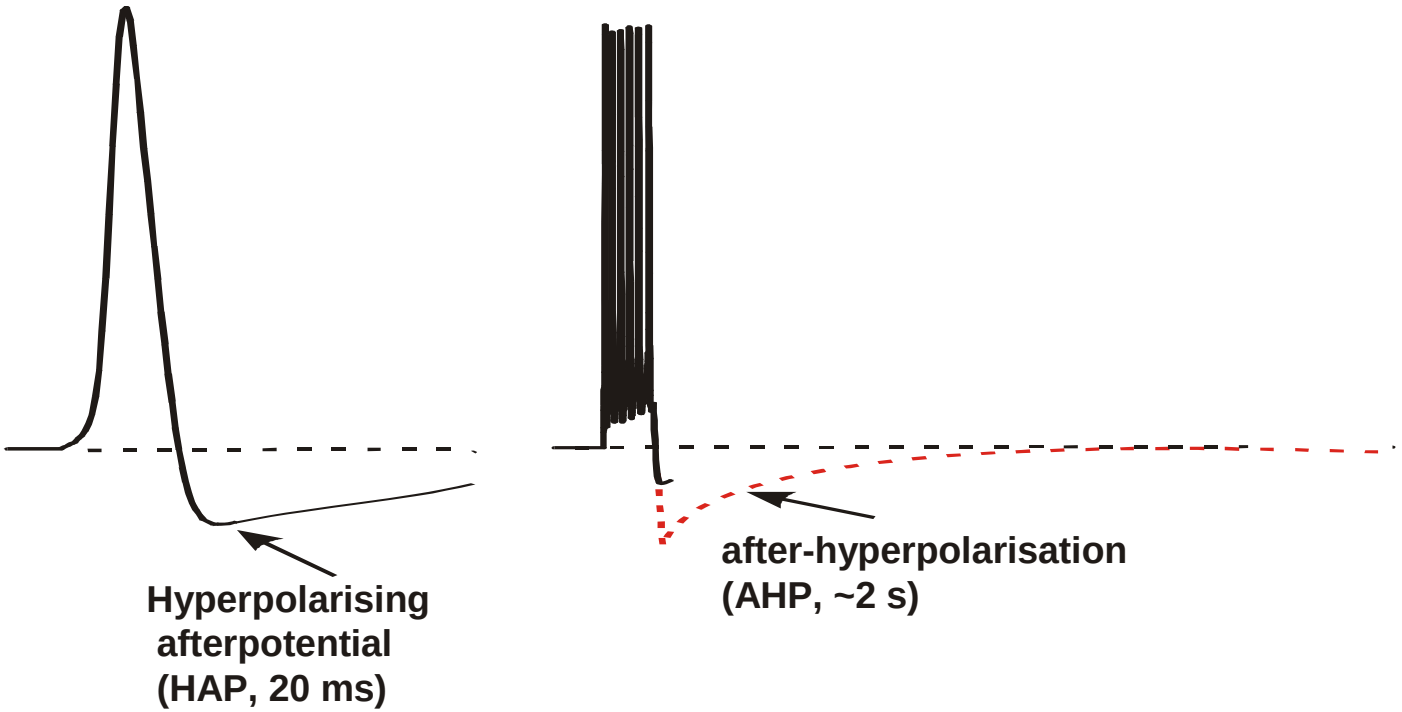


Spontaneous spiking in oxytocin cells is governed by a random (Poisson) process subject to a post-spike refractoriness



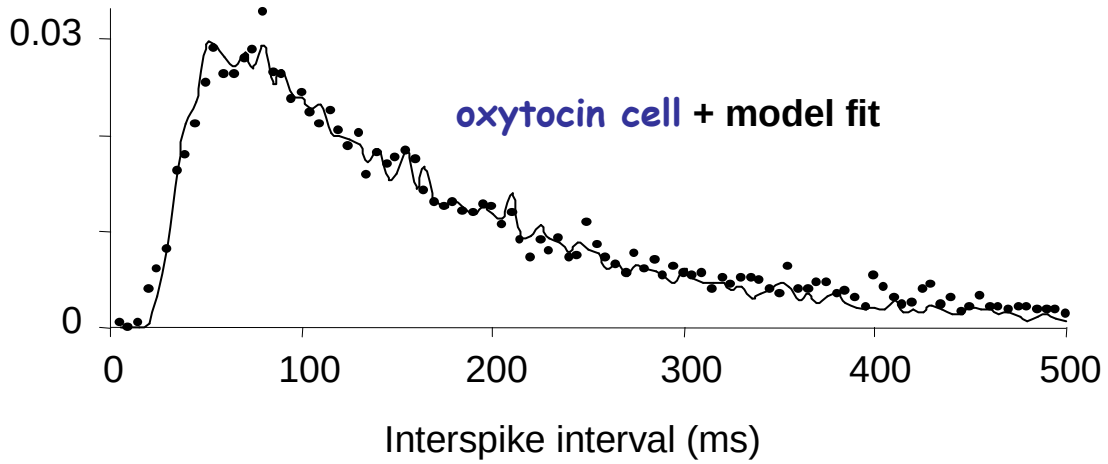


Post-spike potentials

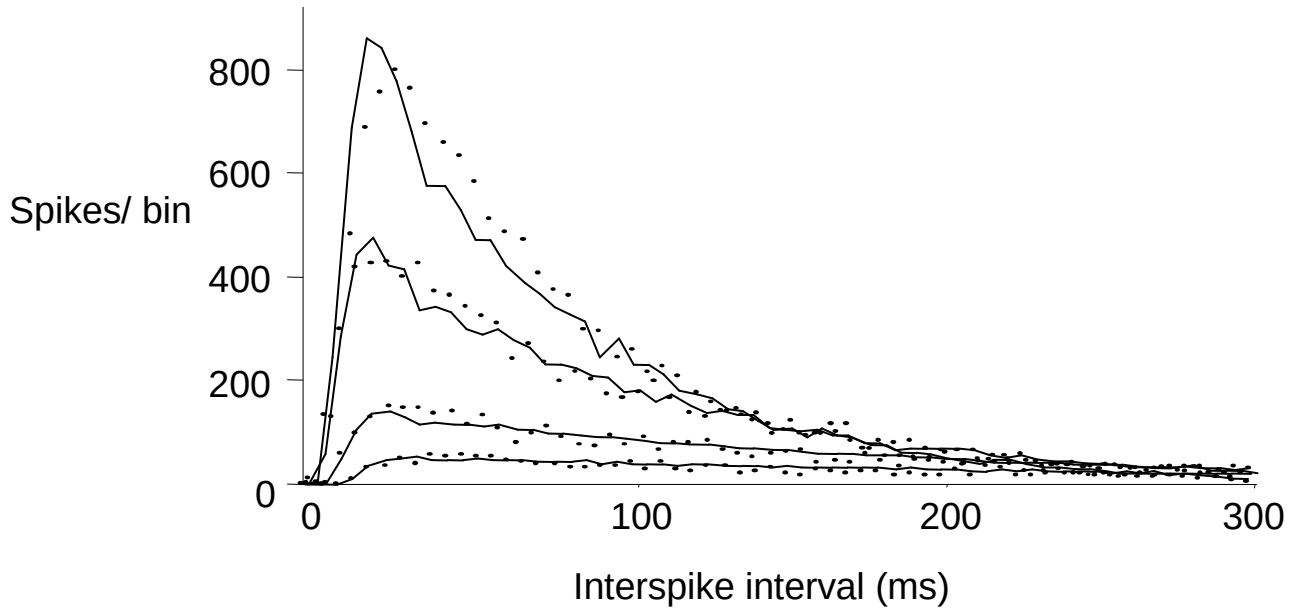


Model parameters

- Spike threshold (mV),
- Resting potential
- EPSP and IPSP height (mV), half-life (ms), rates (/s)
- HAP, described by exponentially decaying change in spike threshold



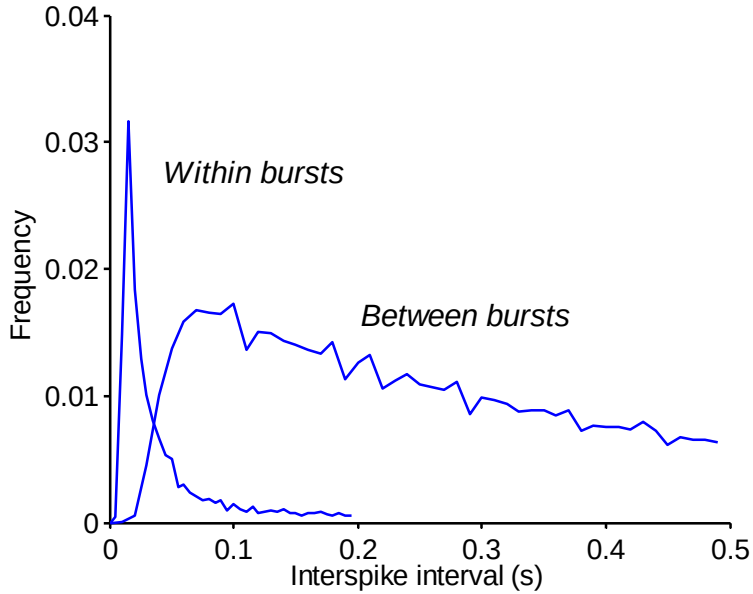
A single model will fit the interspike interval distributions of oxytocin cells at different firing rates following infusion of hypertonic saline

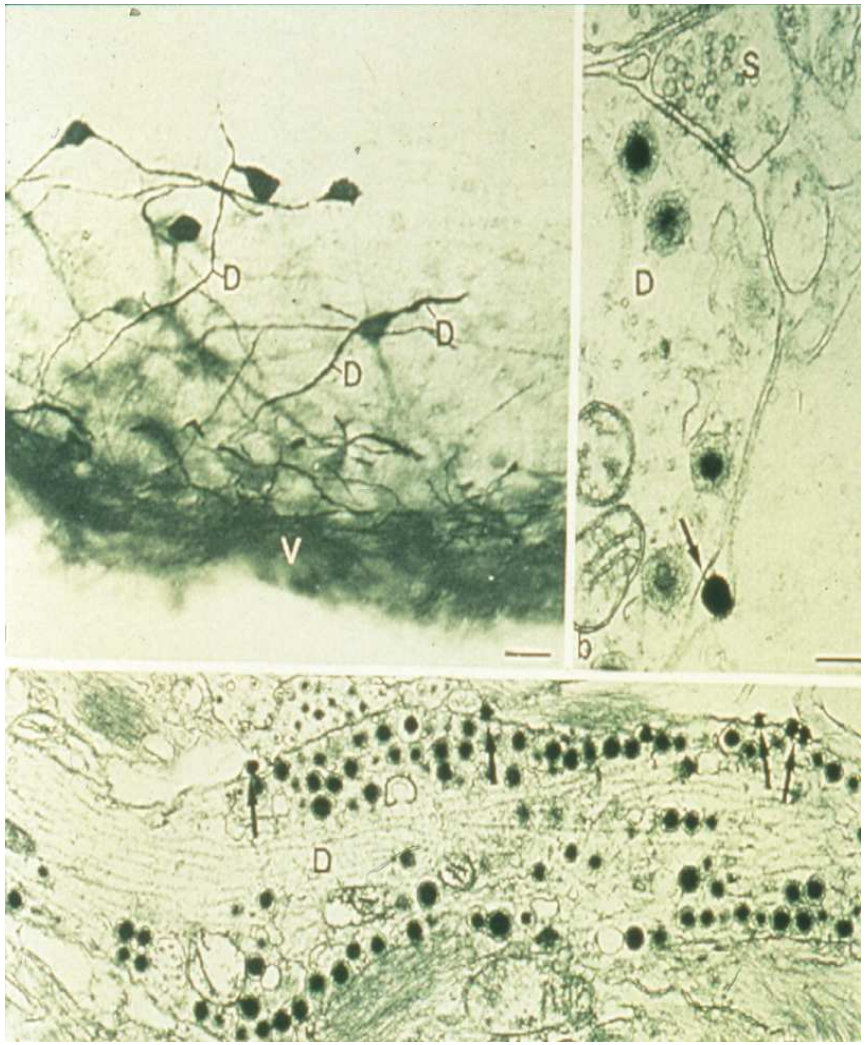


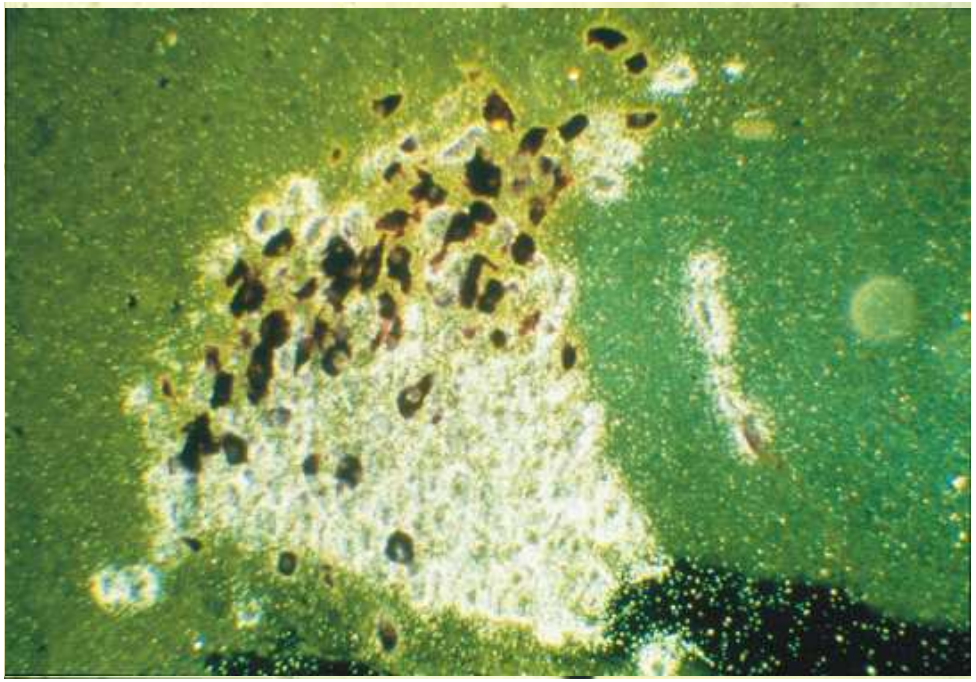
Leng et al. (2001) *J. Neurosci 21:6967-77*

But does this help?

Within bursts, the inter-spike intervals are consistently shorter than almost all intervals seen in other conditions

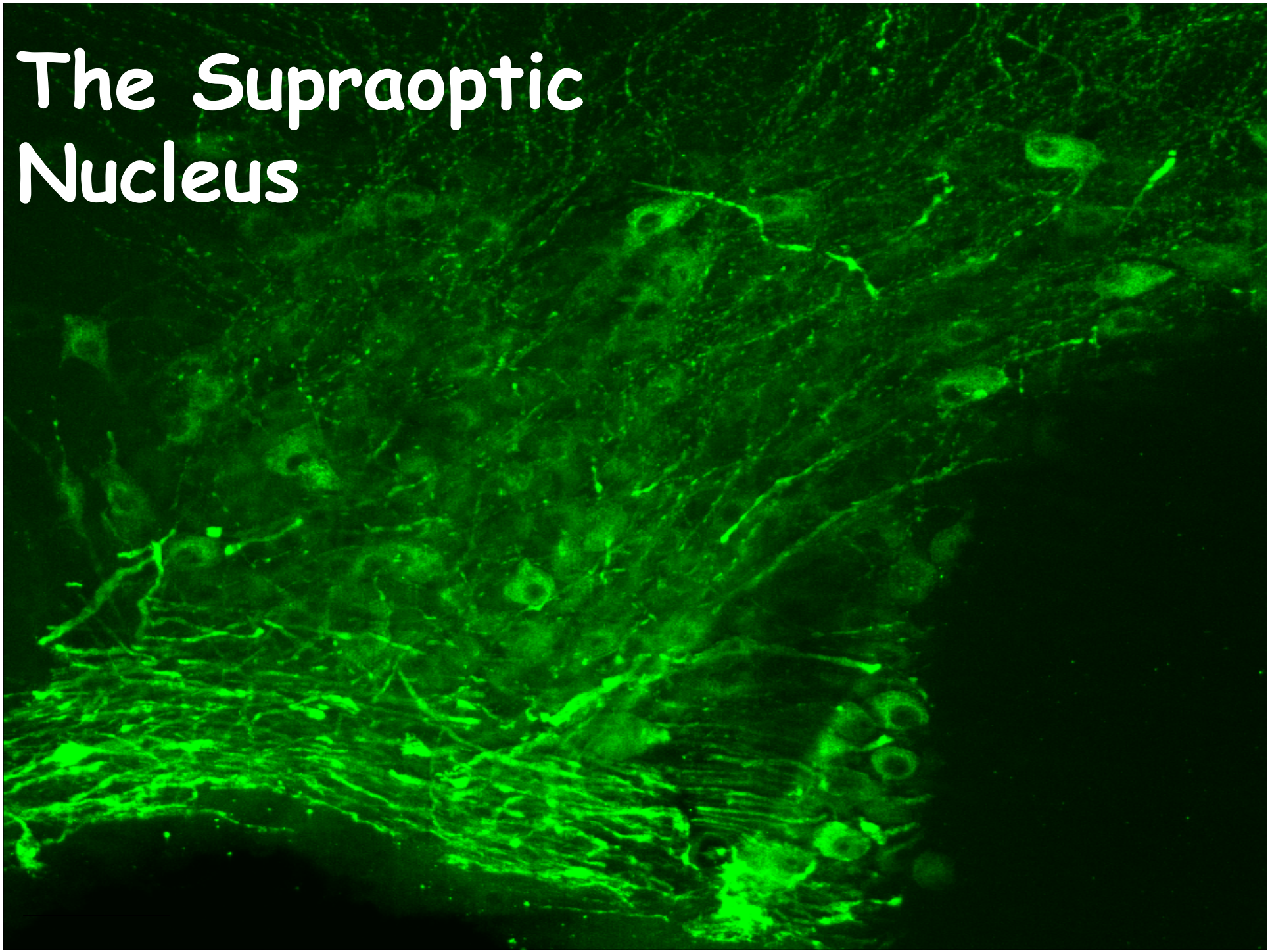






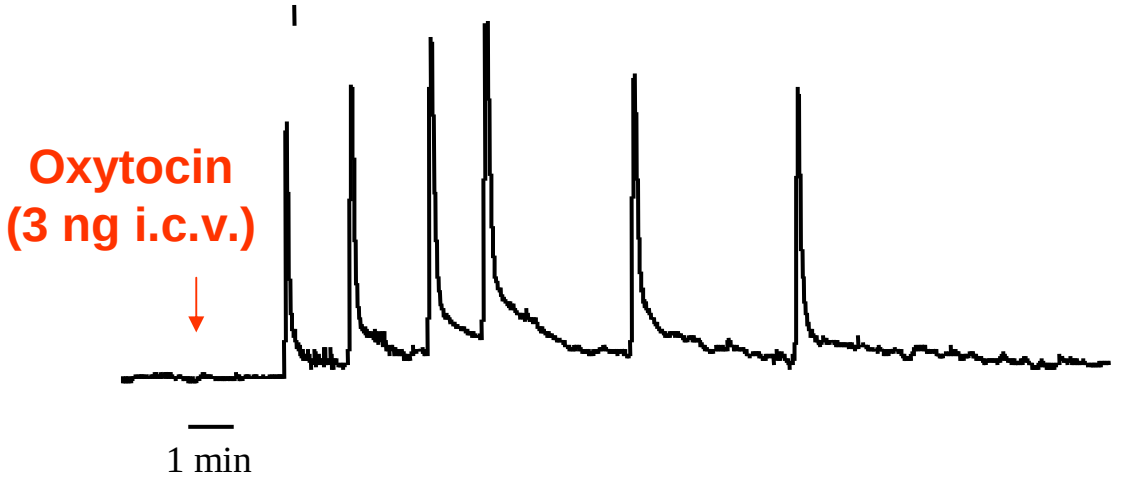
Oxytocin is made in the supraoptic nucleus. These cells send their axons to the pituitary gland, where oxytocin is released into the blood

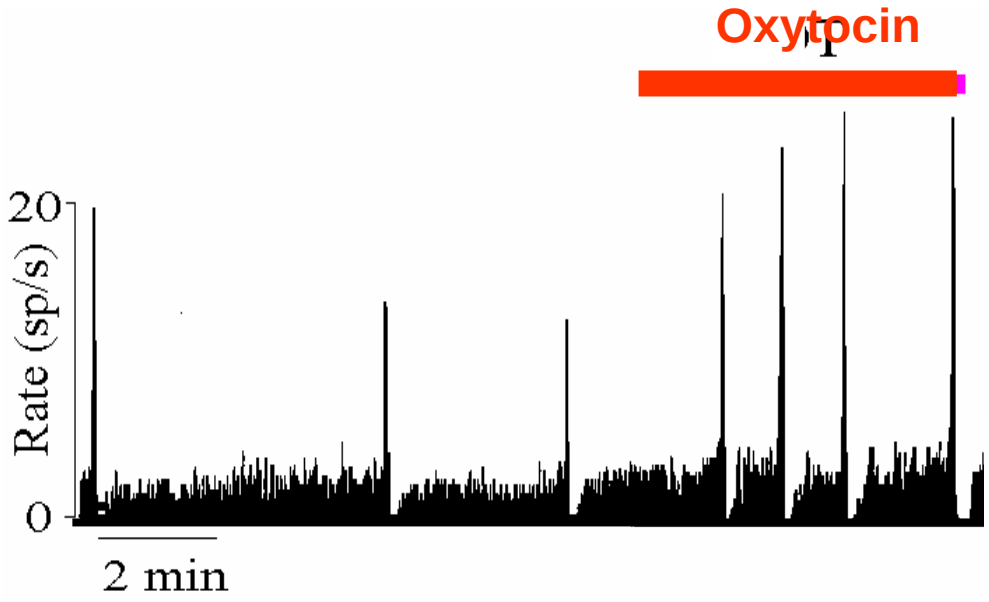
The Supraoptic Nucleus



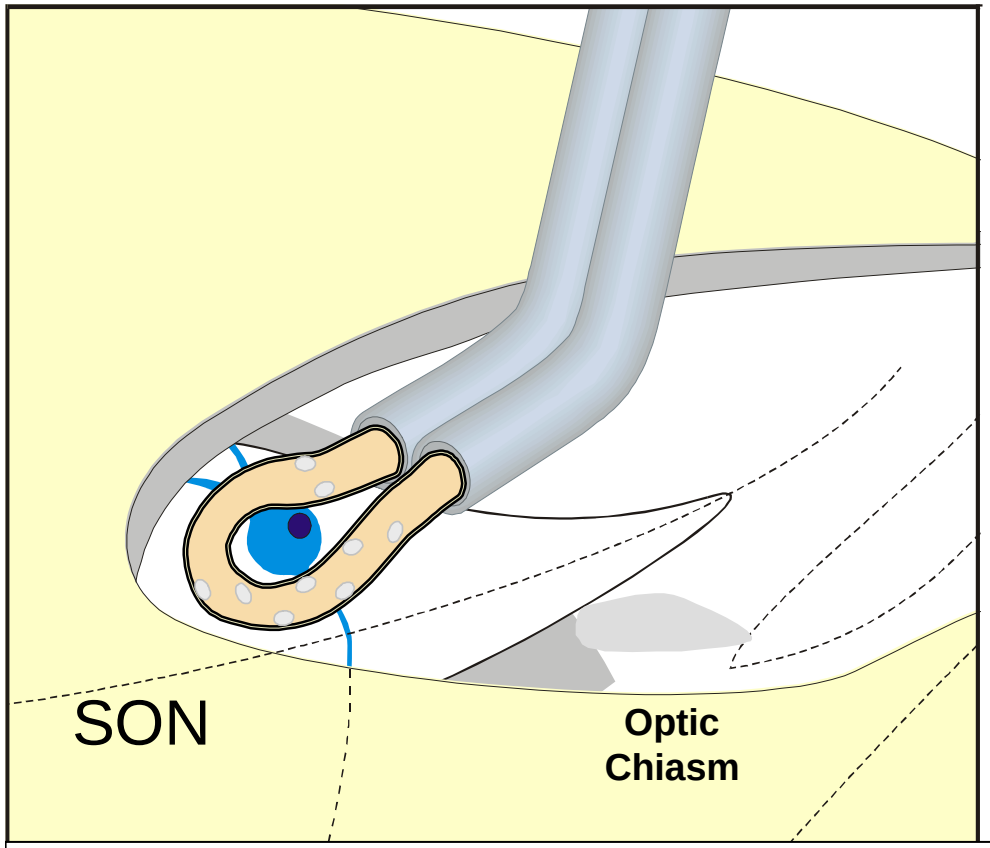
Oxytocin facilitates reflex milk-ejection

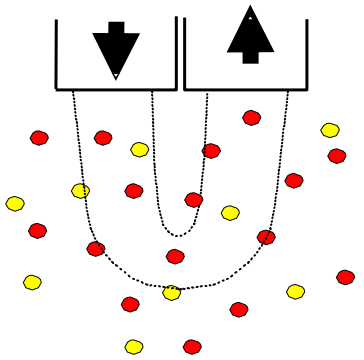
- dendro-dendritic interactions
- dependent on oxytocin release
- apparently a positive-feedback system



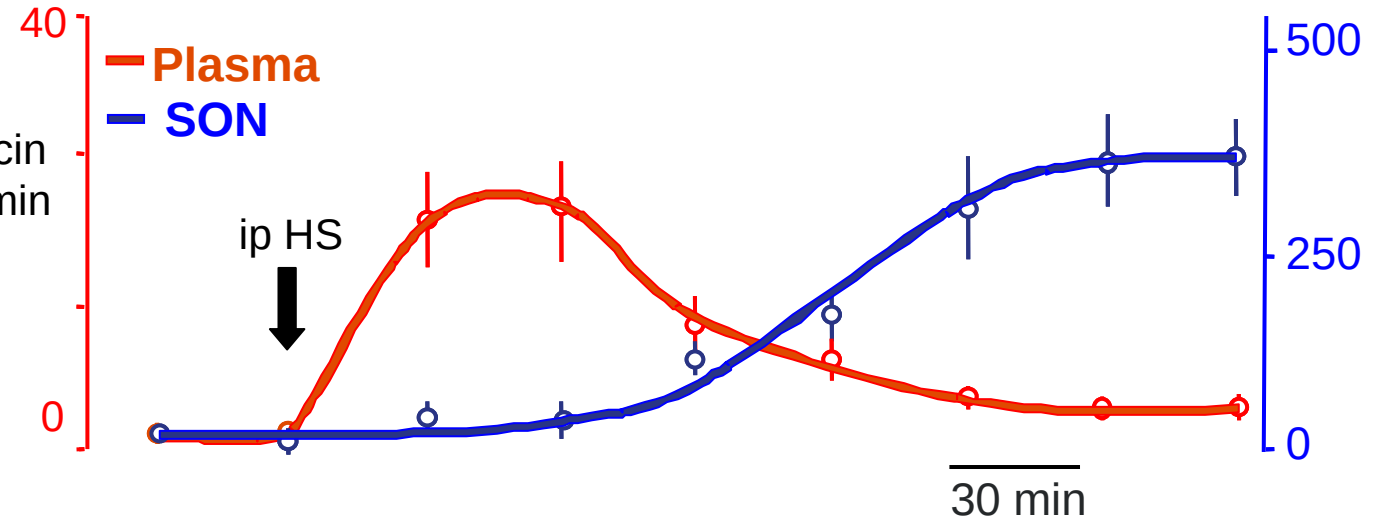


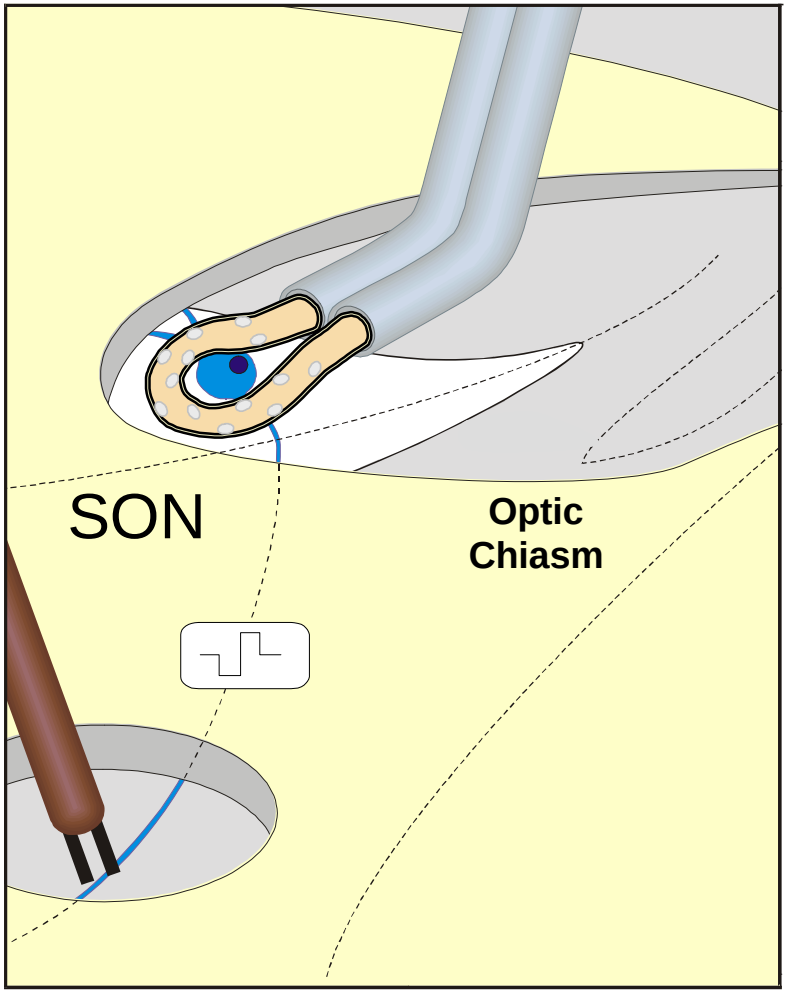
Microdialysis To measure local oxytocin

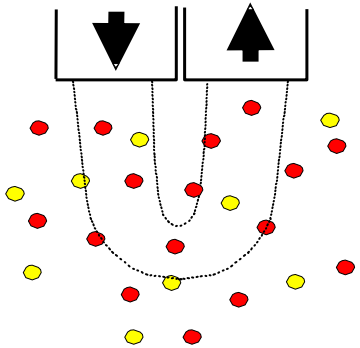


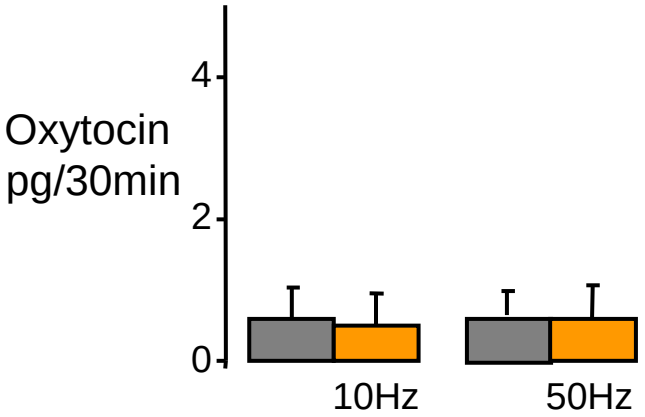


Hypertonic saline

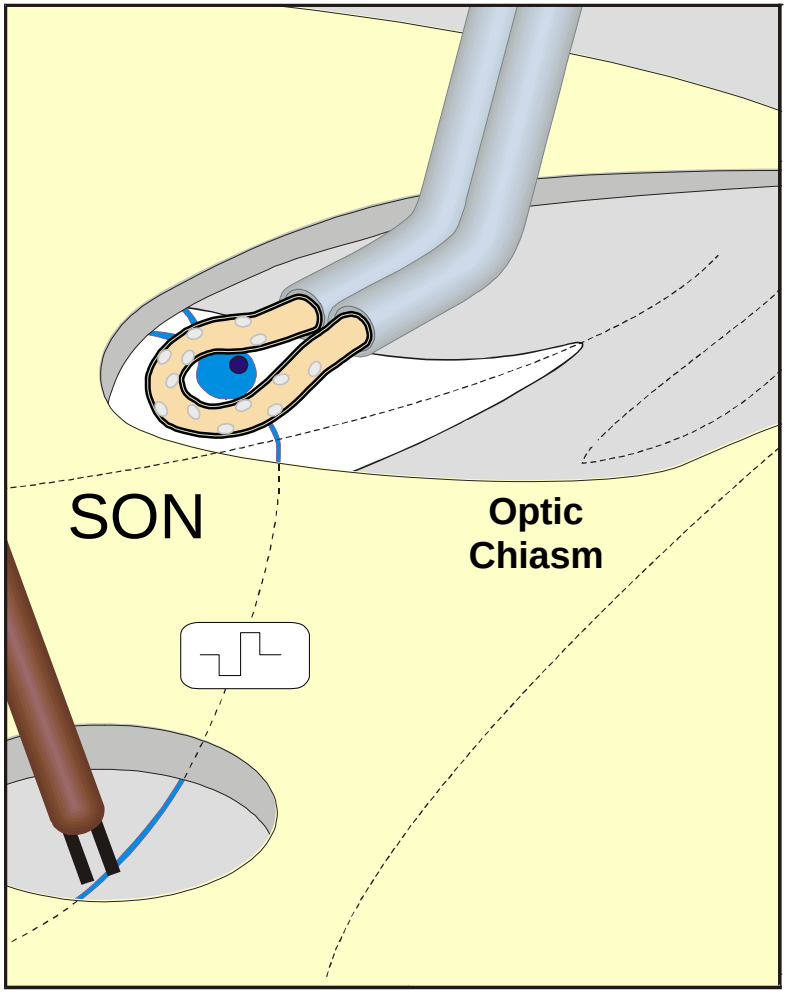


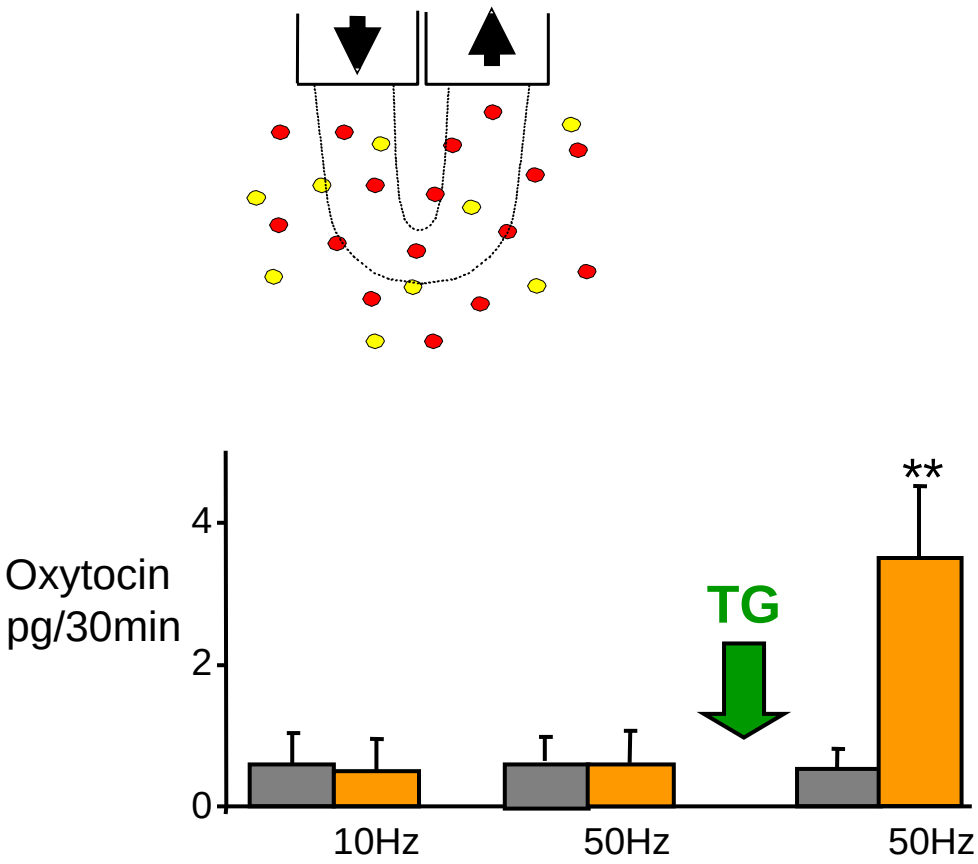






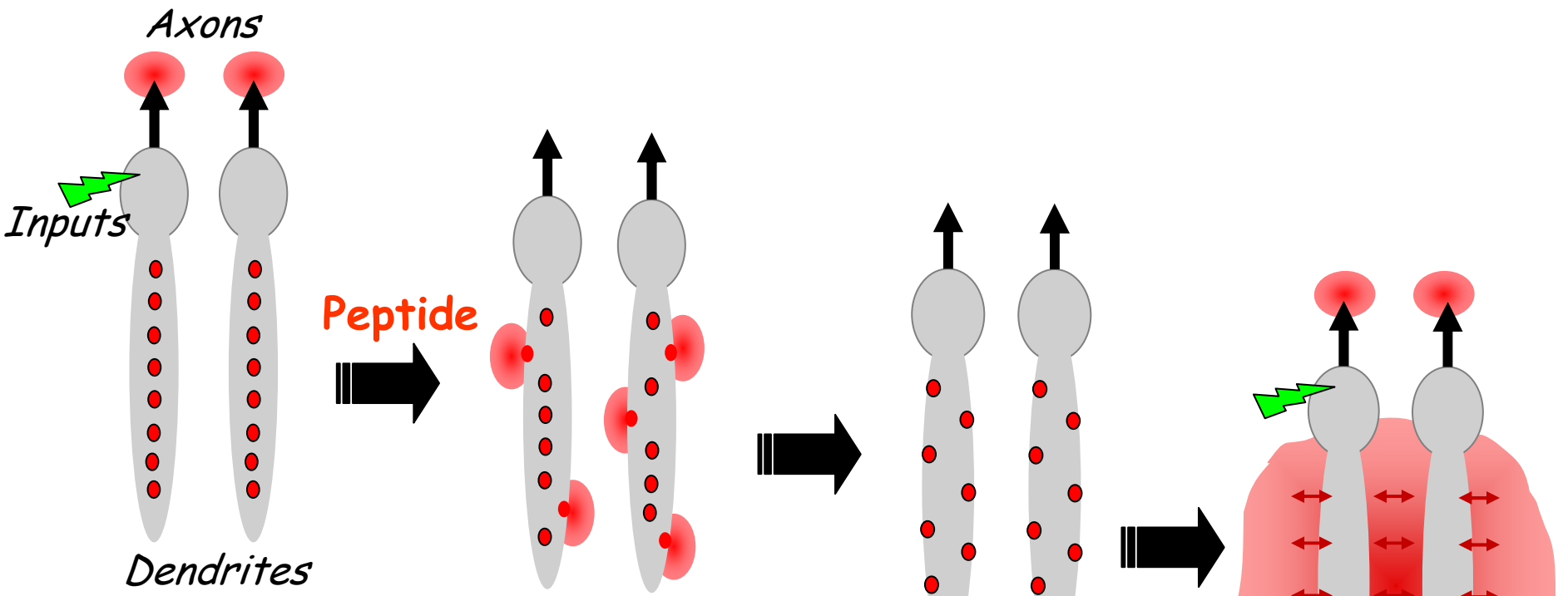
Neural stalk stimulation (spike activity) evokes oxytocin release into blood, but not release from dendrites.





Thapsigargin primes dendritic oxytocin release

(Ludwig et al Nature 2002)



Dendritic release not activated by electrical activity

Peptides trigger release independently of electrical activity and…

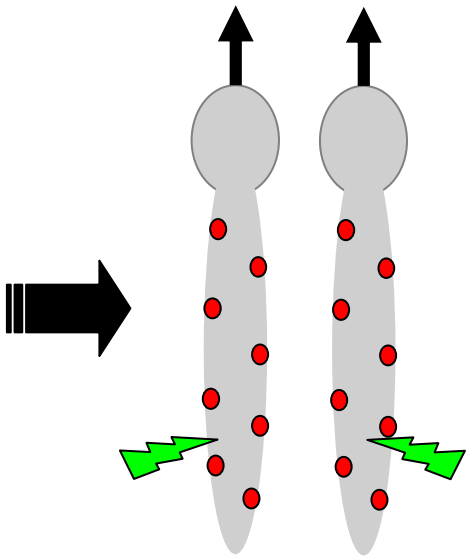
…prime dendritic stores

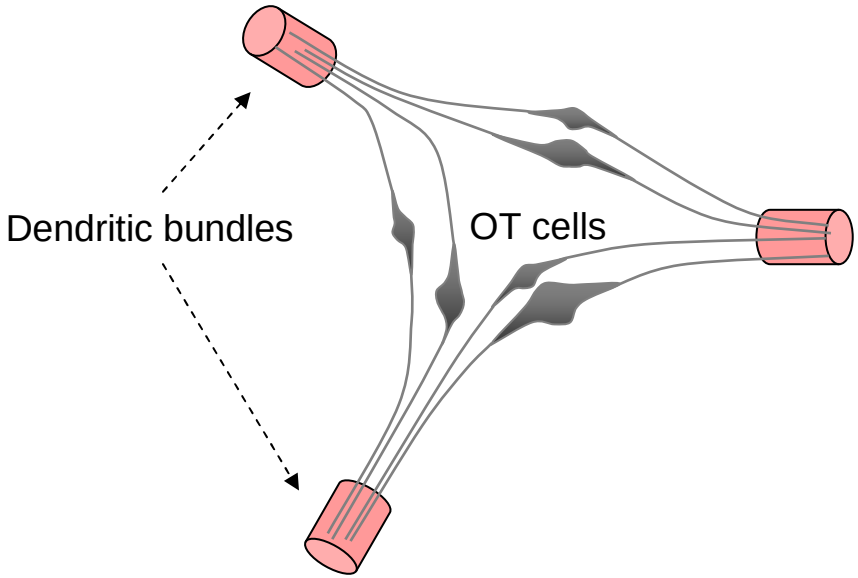
Dendritic release coupled to electrical activity

Priming

Nature (2002) 418.
J. Neurosci. (2003) 23.

Oxytocin cells, coupled via dendrites

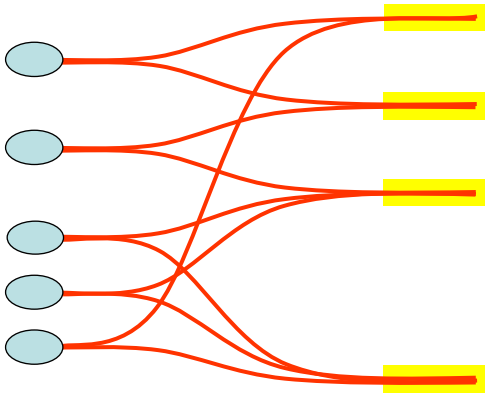


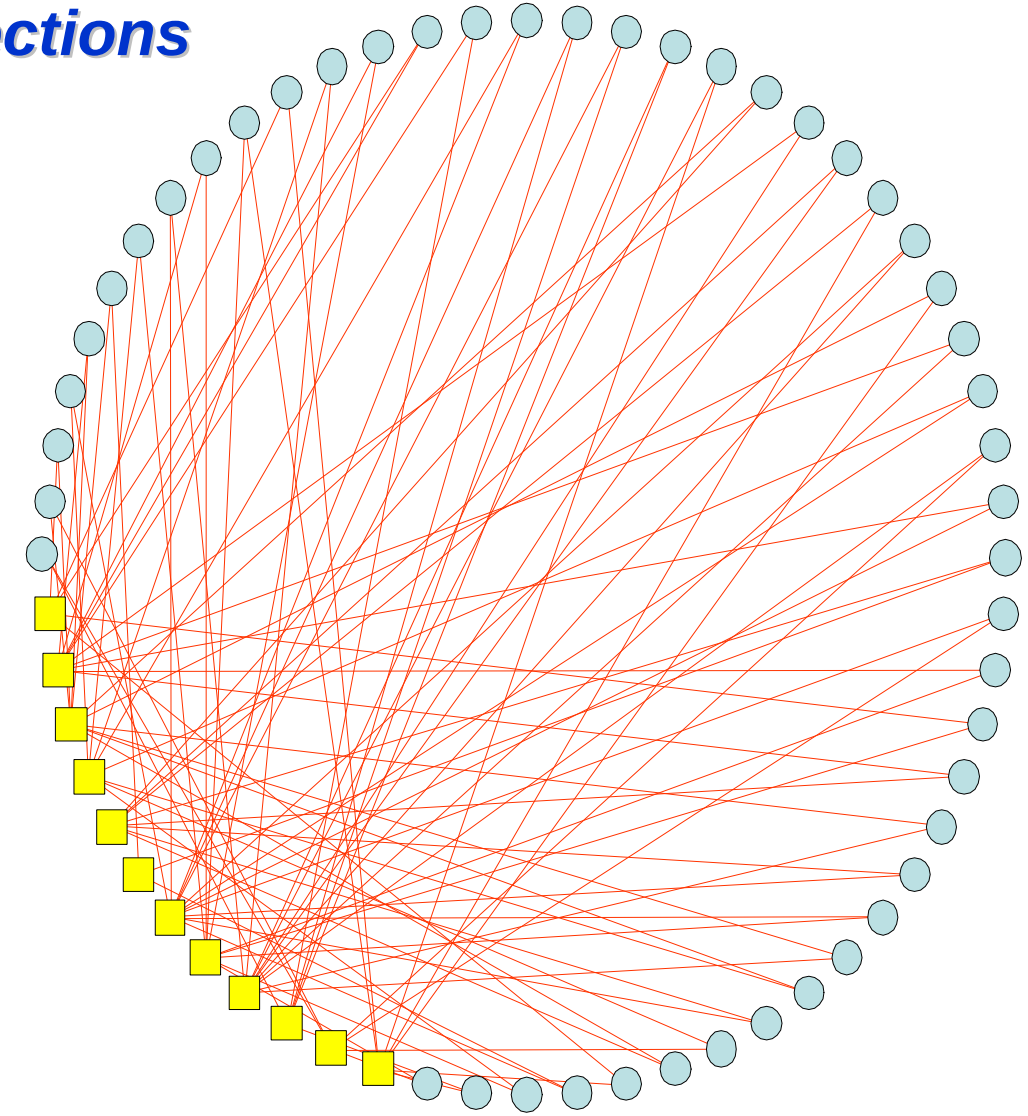


~3000 oxytocin cells
~2 dendrites per cell
Each dendrite is part of a bundle of 3-5 dendrites
Each cell connected to ~8 others

Initial network had just 15 cells; current network has 384 cells

Dendro-dendritic connections



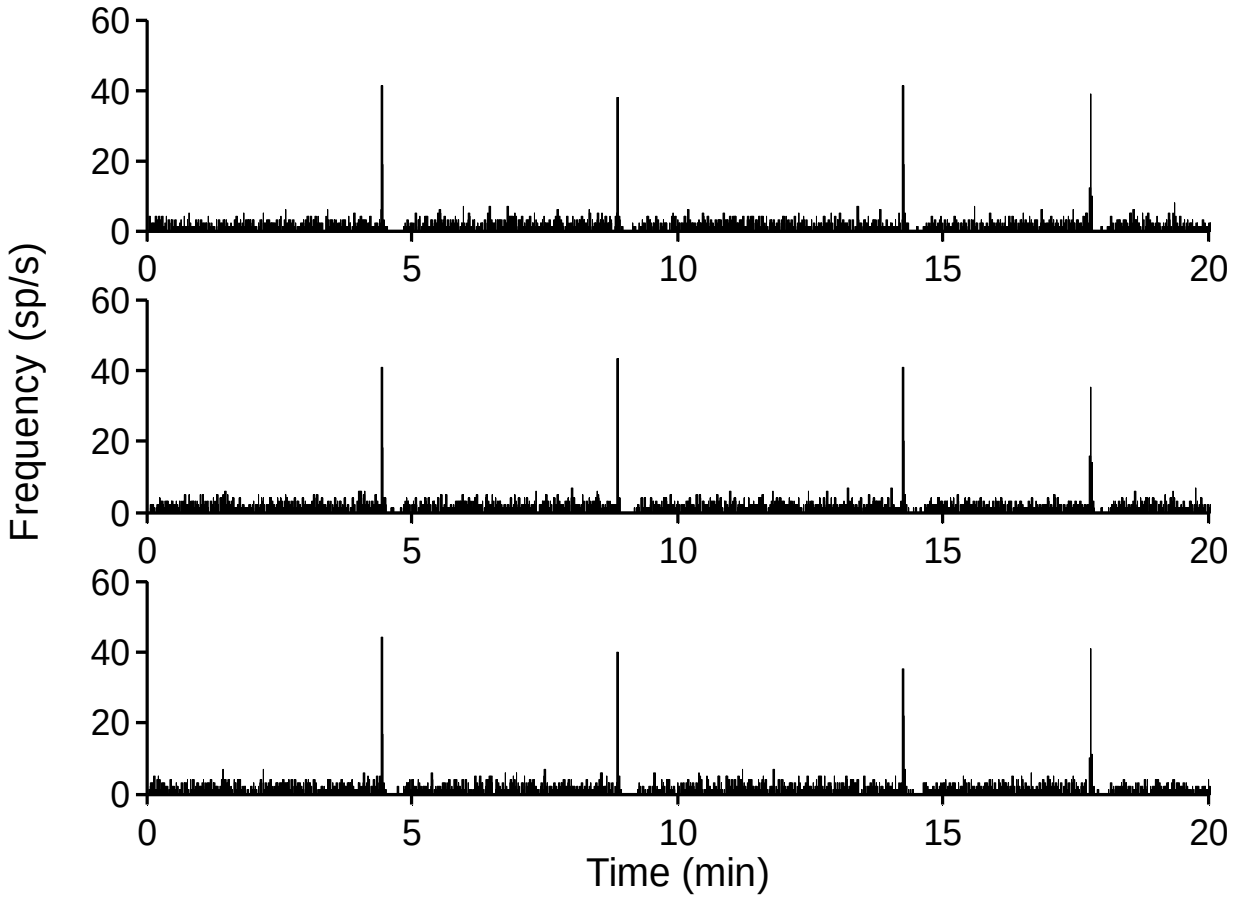


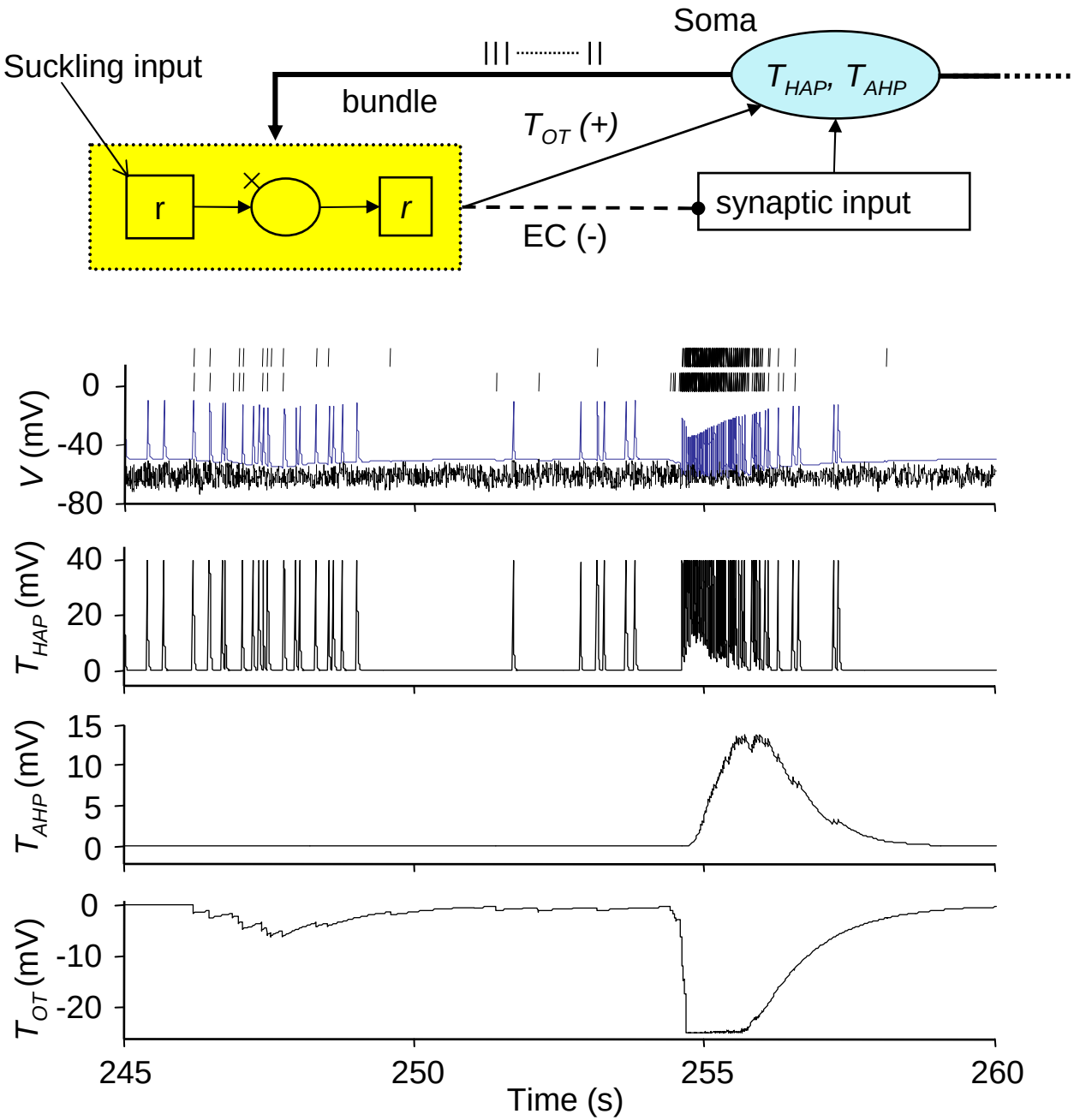
Sparse and random

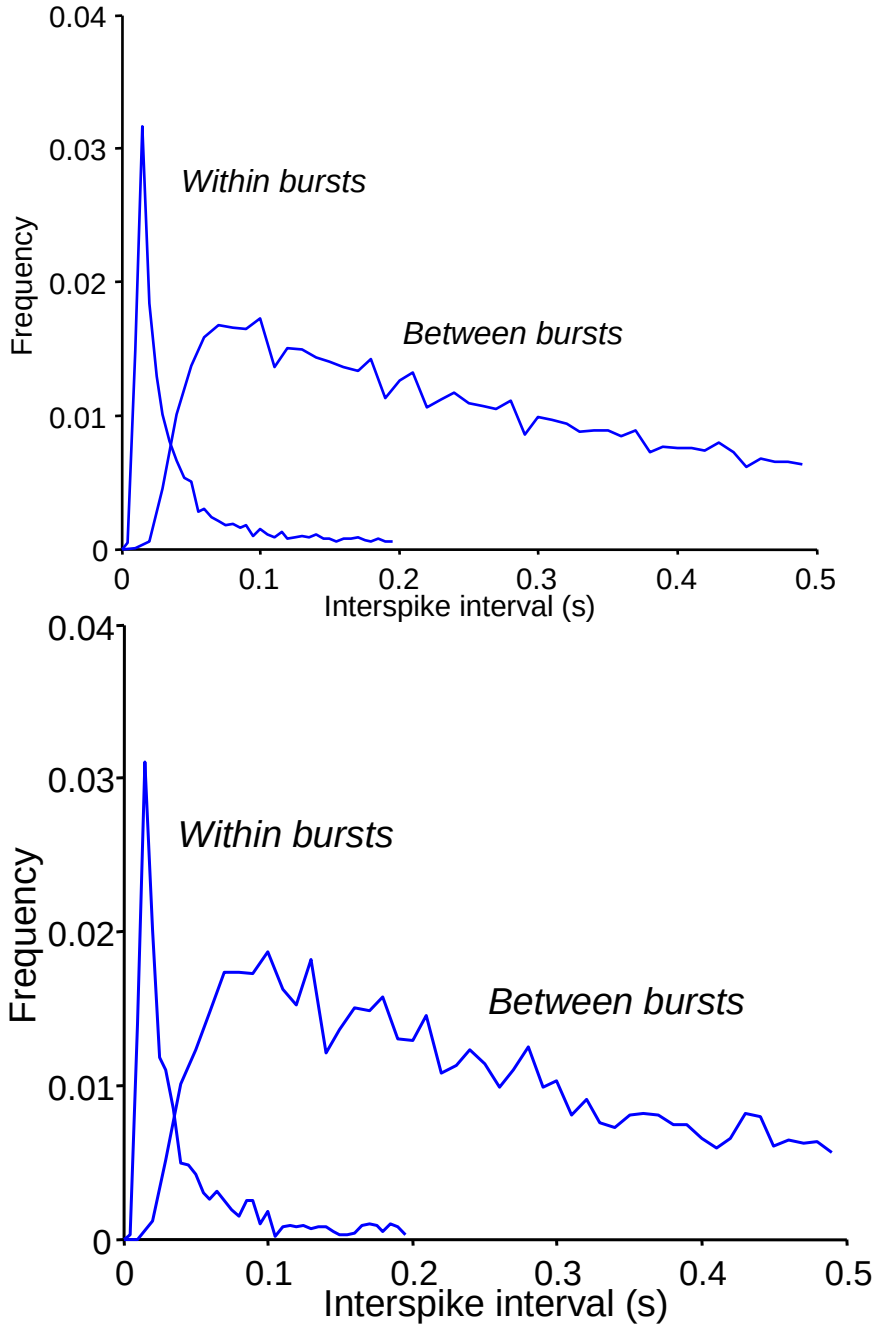
EMERGENT BEHAVIOUR

Behaviour in a complex non-linear system that arises "spontaneously" above a critical level of complexity

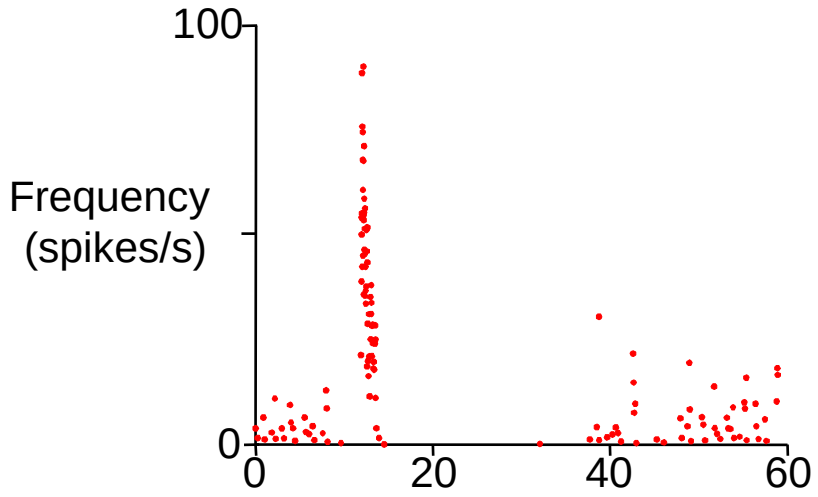
Bursting in the model

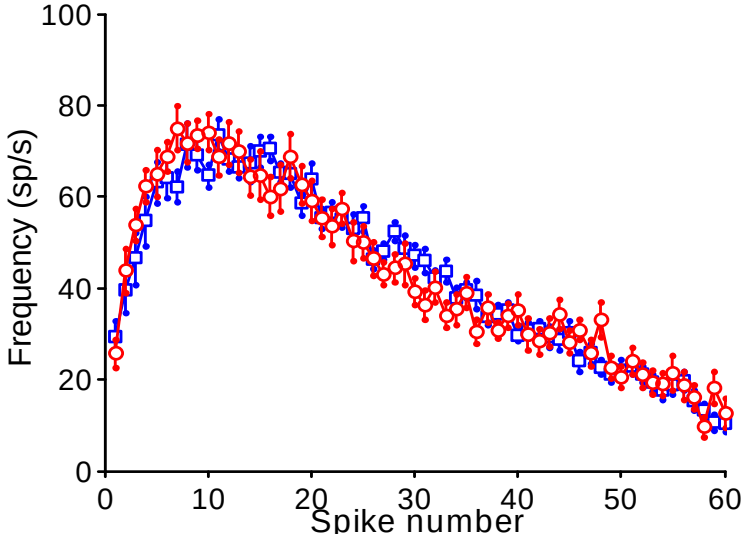


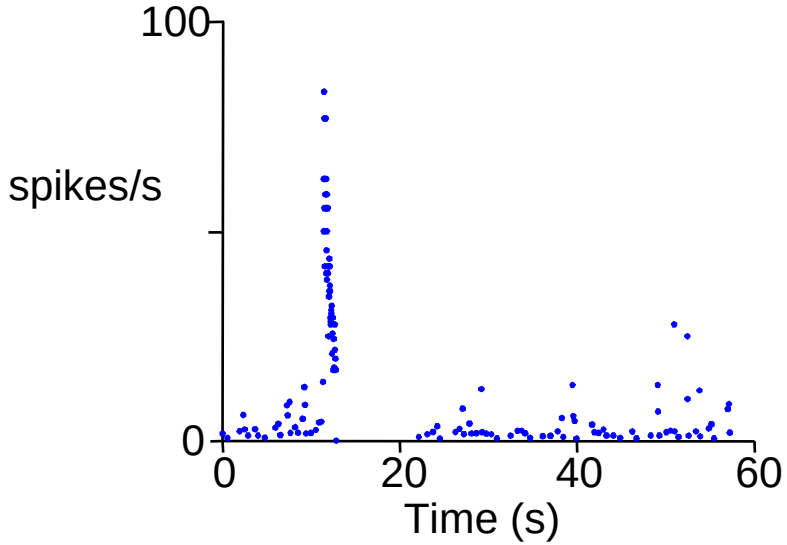

Soma
Suckling input
bundle
T_{HAP}, T_{AHP}
T_{OT} (+)
r
r
synaptic input
EC (-)
V (mV)
0
-40
-80
T_{HAP} (mV)
40
20
0
T_{AHP} (mV)
15
10
5
0
T_{OT} (mV)
0
-10
-20
245
250
255
260
Time (s)

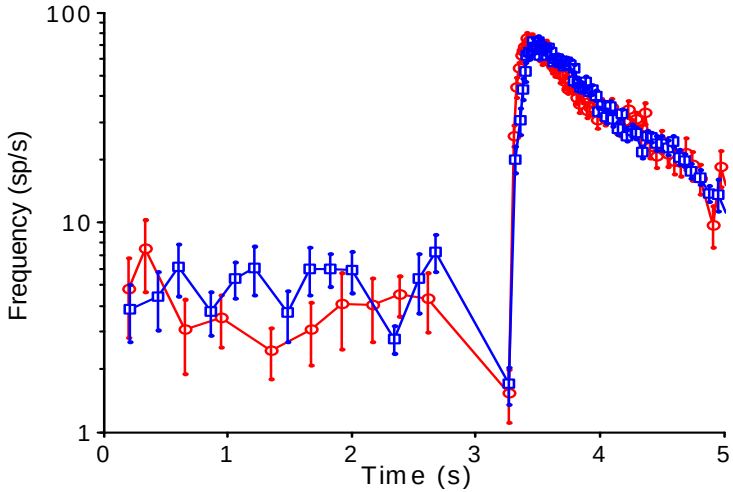

0.04
0.03
0.02
0.01
0
Frequency
Within bursts
Between bursts
0
0.1
0.2
0.3
0.4
0.5
Interspike interval (s)
0.04
0.03
0.02
0.01
0
Frequency
Within bursts
Between bursts
0
0.1
0.2
0.3
0.4
0.5
Interspike interval (s)

Milk-ejection bursts; experiment and model





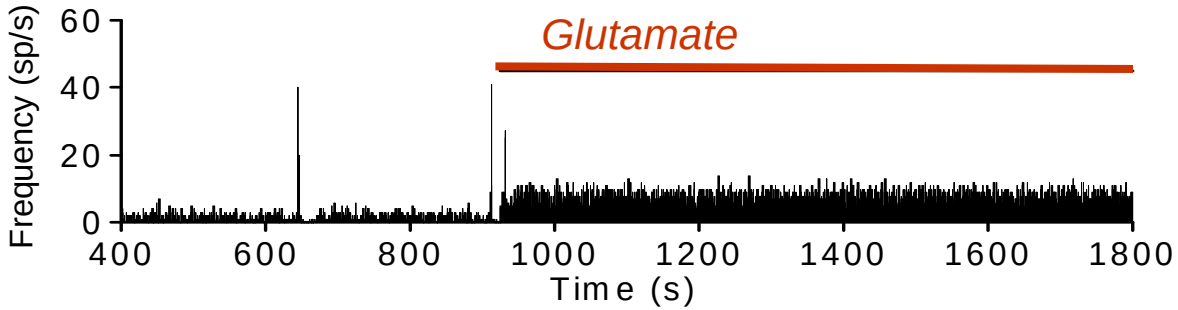




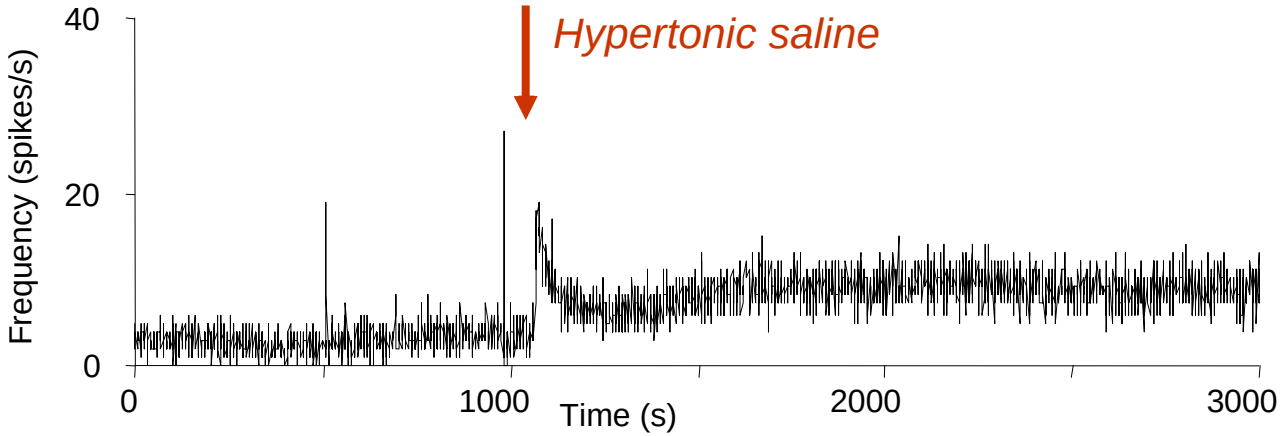
Increasing the excitatory input rate in the model … results in the termination of bursting

40% increase in excitatory input

Model



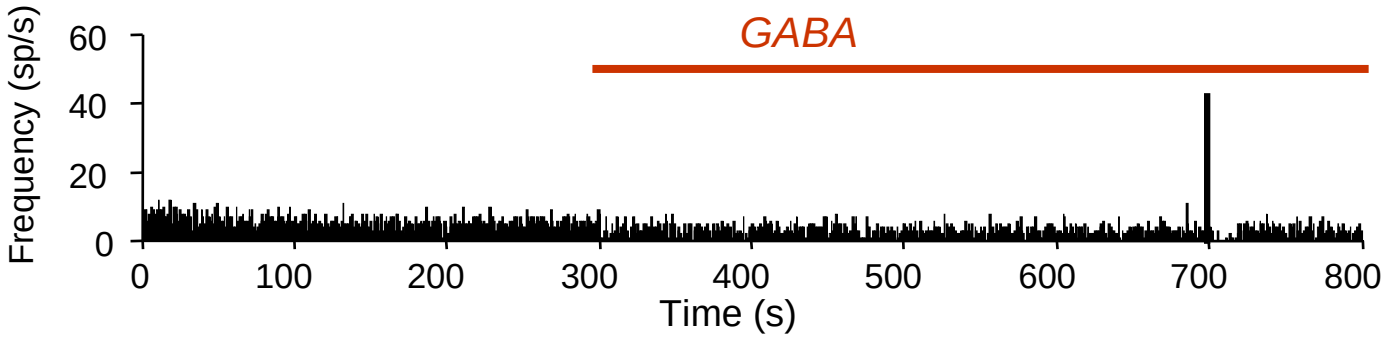
In vivo



Moos, J. Physiol., 1995

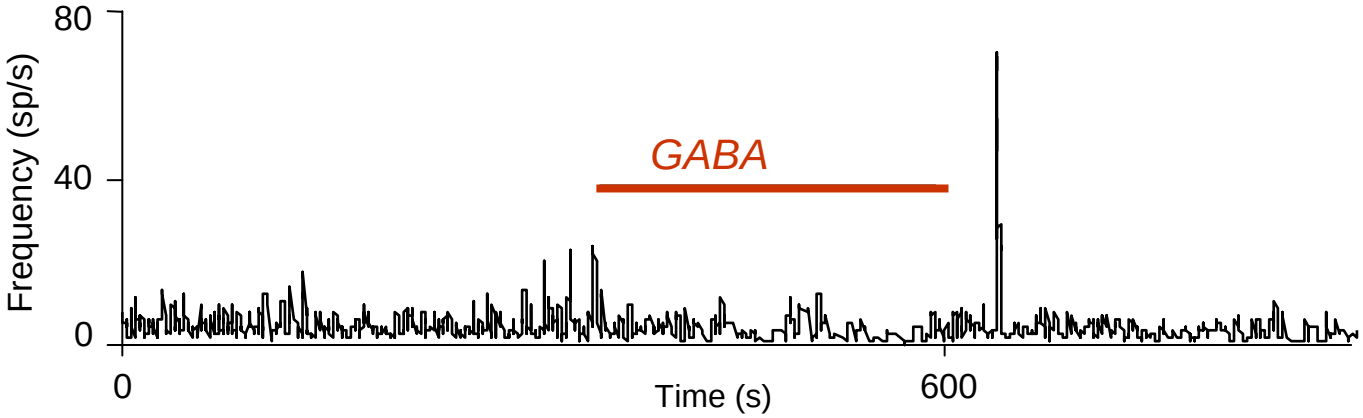
Enhancing inhibitory activity promotes bursting

Model



This paradoxical effect of triggering milk-ejection bursts was also described in vivo

In vivo



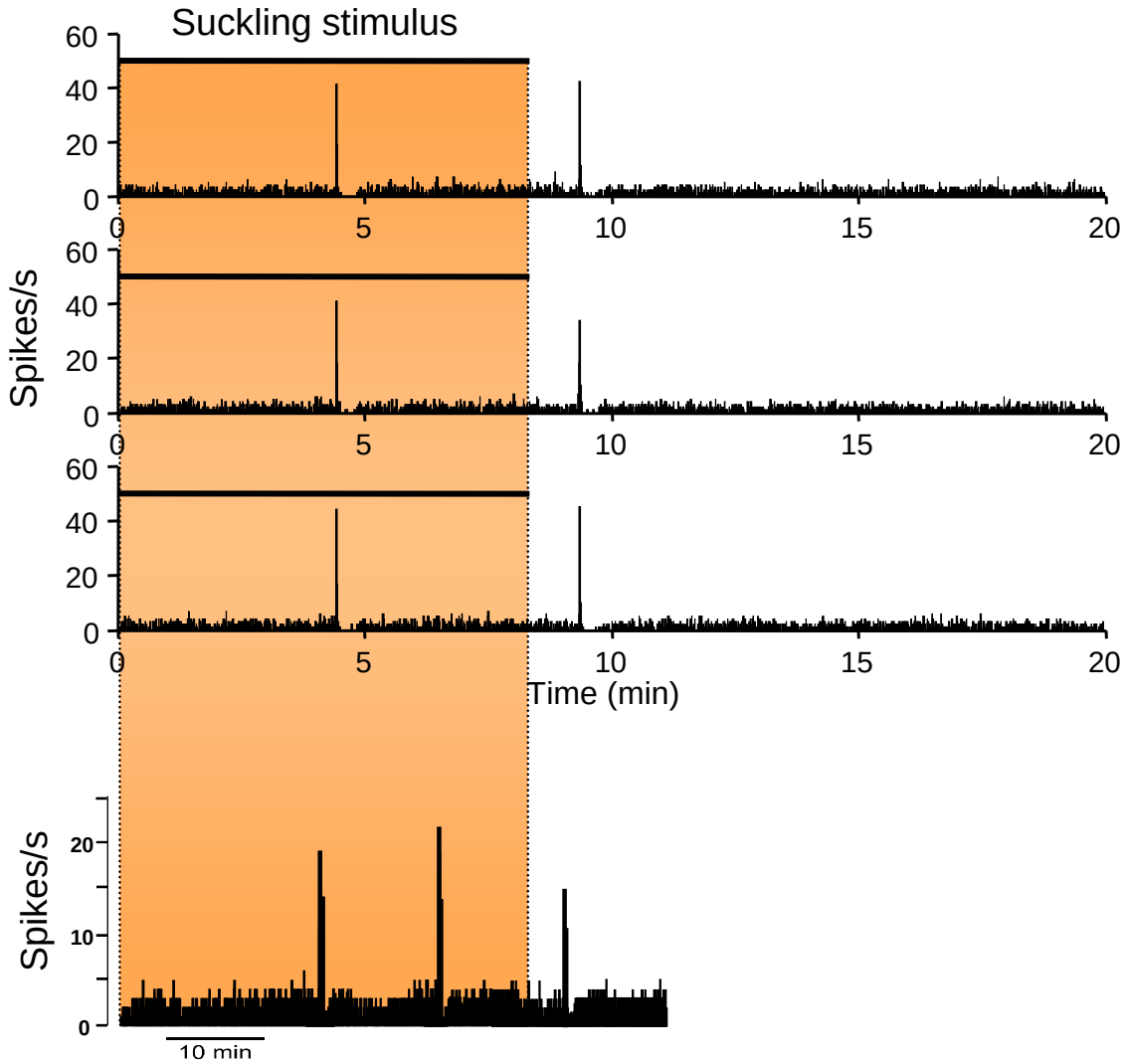
Moos, J. Physiol., 1995

Suckling is necessary for bursting….

but a single burst can occur after the pups are removed

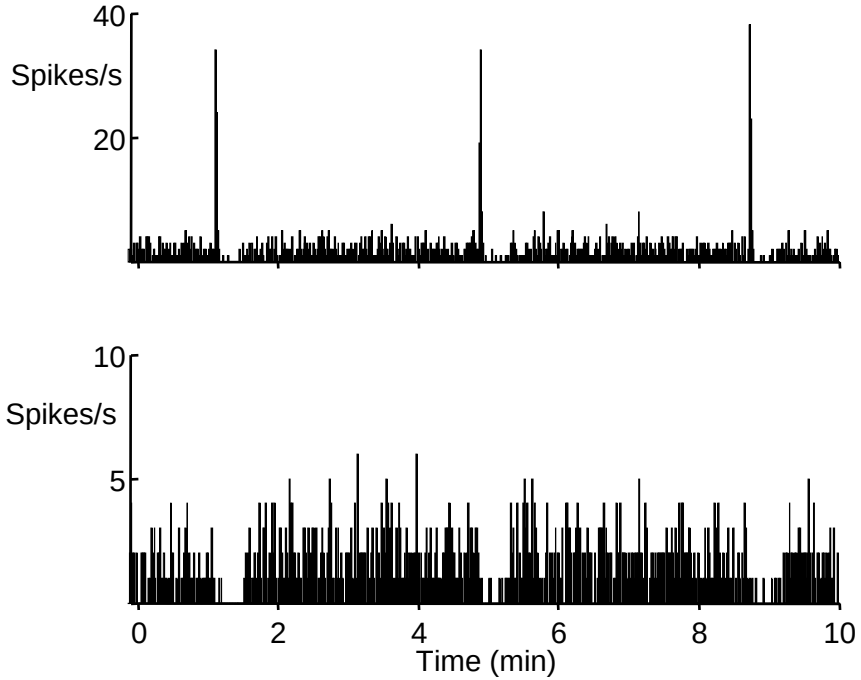
Model

In vivo

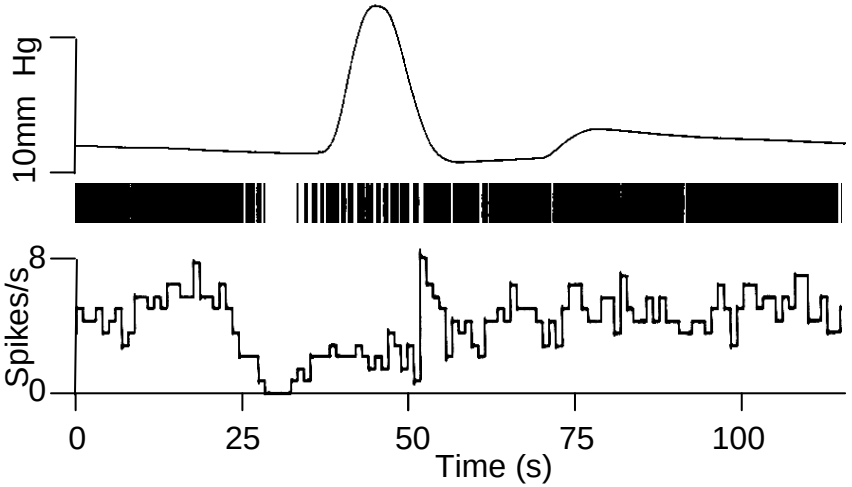


Suppressing afferent excitation by OT silences OT cells

Model



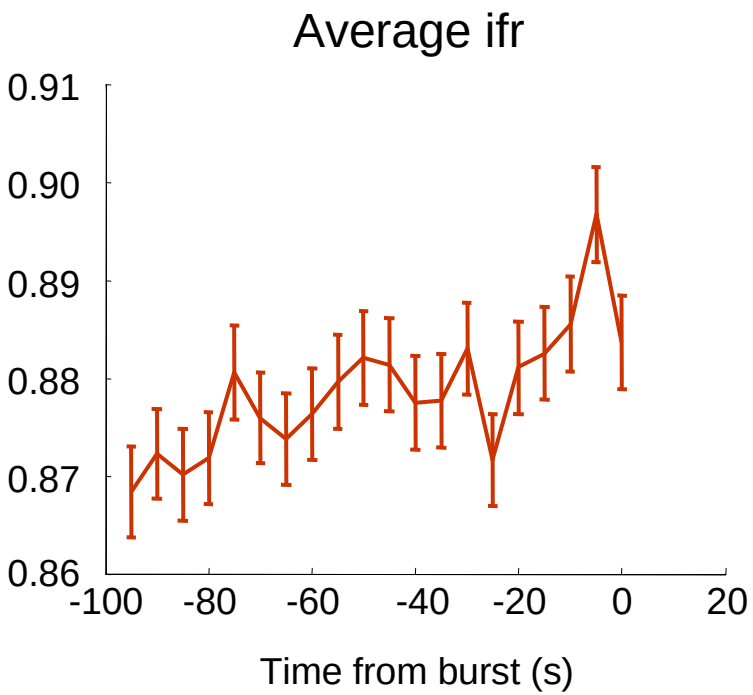
In vivo

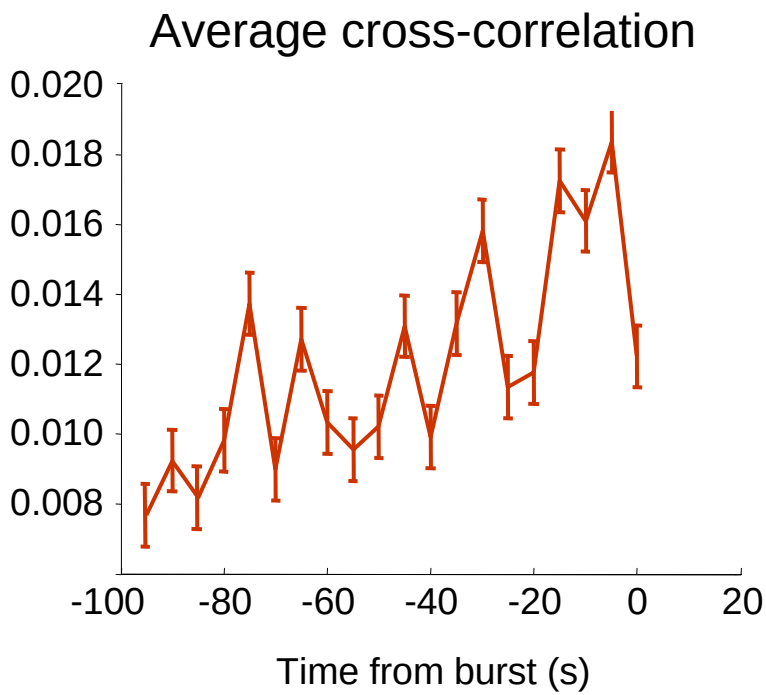


no burst activity preceding milk ejection but typical "post burst" silence

post- burst silence is not simply a consequence of activity-dependent AHP

Activity becomes more irregular
and more cross-correlated approaching bursts





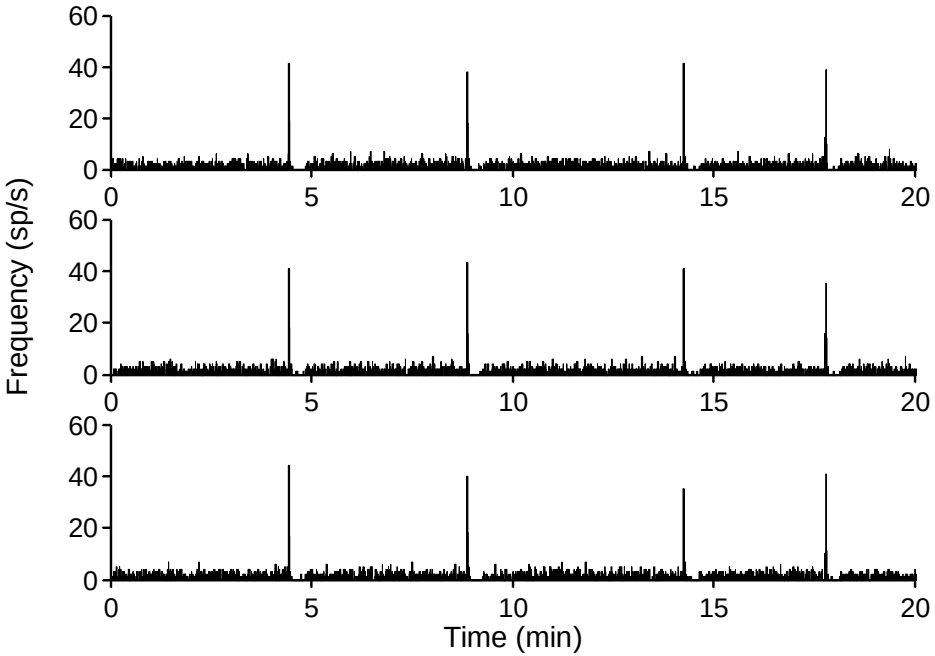
: consequence of the progressive strengthening of the interactions between neighbouring cells in the network topology

Mean of 136 bursts, 48 cell network, 8 dendrites per bundle

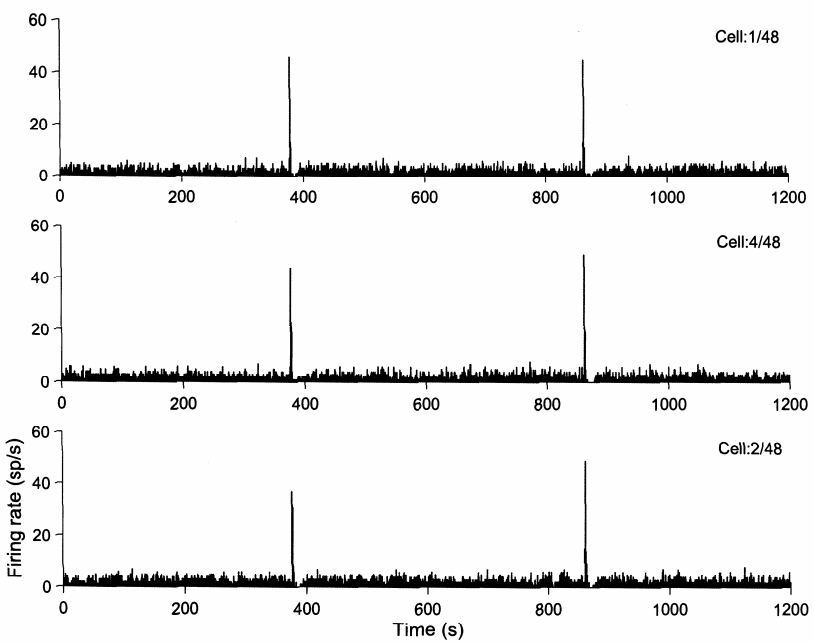
Random connectivity is essential...

Modifying the mean number of dendrites per bundle affects bursting

8 dendrites/bundle

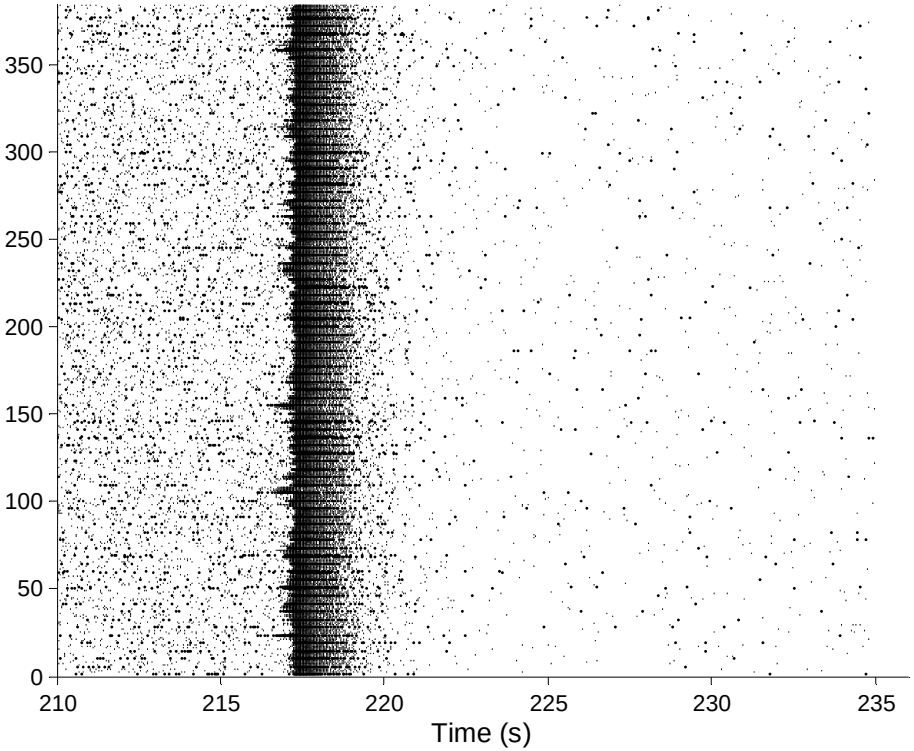


3 dendrites/bundle

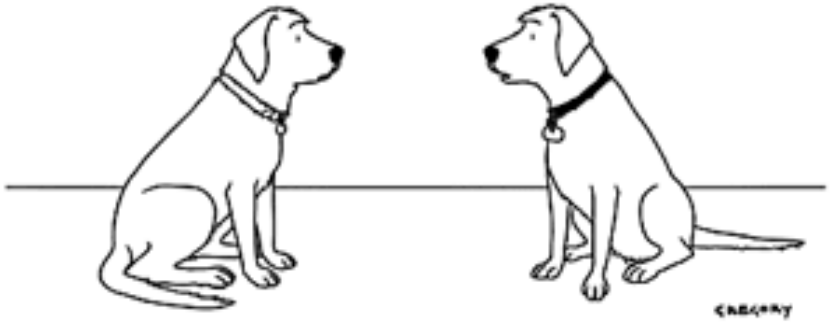


A minimum of 8 random connections are needed
to ensure that OT cells are all interconnected

Random connectivity is essential...



Synchronous activation of release within the brain will lead to a “tidal wave” of oxytocin through the forebrain



"I had my own blog for a while, but I decided to go back to just pointless, incessant barking."

- Peptide release from a given nerve ending is very rare
- The peptide released at a single event is much more than needed for synaptically localised action
- Peptides are very long lasting
- Peptides can “bind neurones together” into co-ordinated activity
- This can lead to co-ordinated peptide release that can spread to distant targets
- Peptides affect the functional wiring of neuronal circuits

- **They re-programme the brain**.

In the brain….

- The hypothalamus has 9000 oxytocin cells and ~12 ng oxytocin – in ~11,000 vesicles per cell.
- 1 vesicle released/cell every 1000s = ~0.001 pg/s.
- If the half-life is **30s**, and the distribution volume of ECF is **1µl** (i.e. ~the whole hypothalamus)….
- This will sustain an ***average*** concentration of **>50 pg/ml** (throughout the hypothalamus).
- Effective concentrations in the periphery are ~ 10 pg/ml

Before

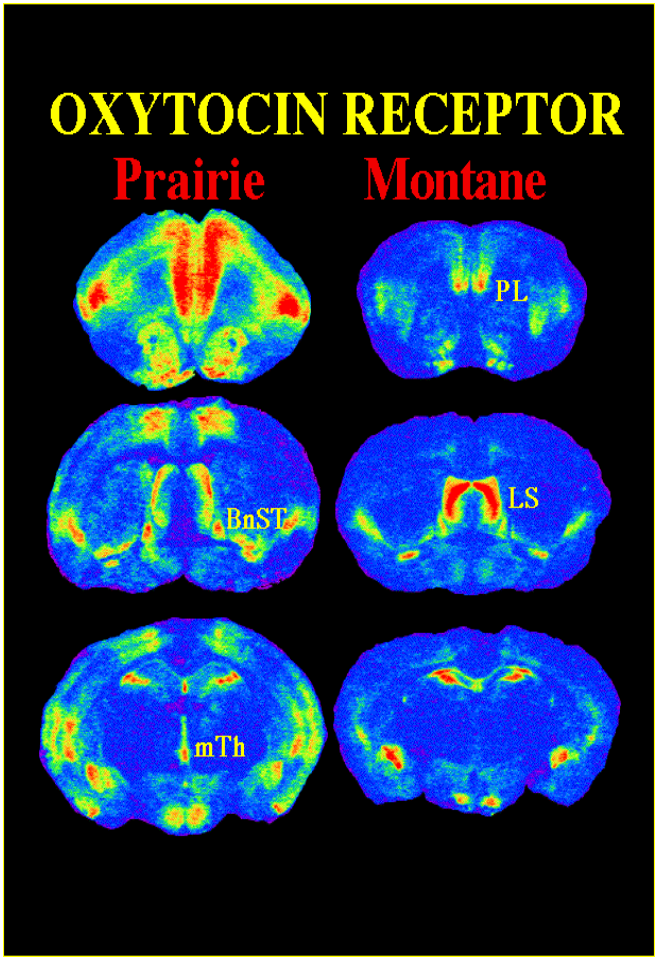
During labour, oxytocin can trigger **maternal behaviour**

After

Oxytocin may have a role in
bonding between sexual partners

Prairie Vole

Sociable
Biparental
Monogamous



Montane Vole

Antisocial
Minimally Parental
Promiscuous


What we say to dogs
Okay, Ginger! I've had it! You stay out of the garbage! Understand, Ginger? Stay out of the garbage, or else!
what they hear
blah blah GINGER blah blah blah blah blah blah GINGER blah blah blah blah blah...
Larson