Osmoresponse in oxytocin neurones
A predictive computational model

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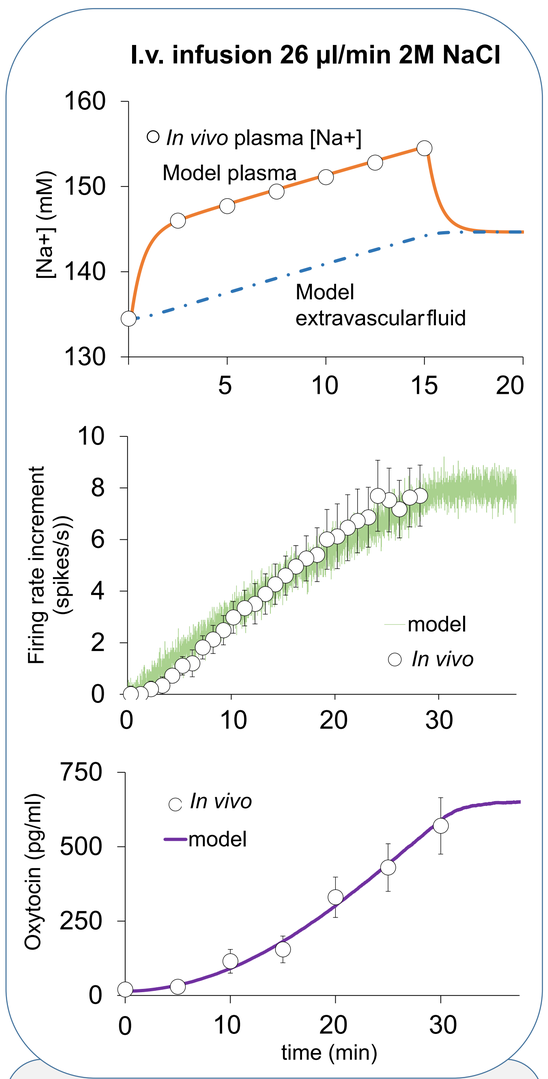
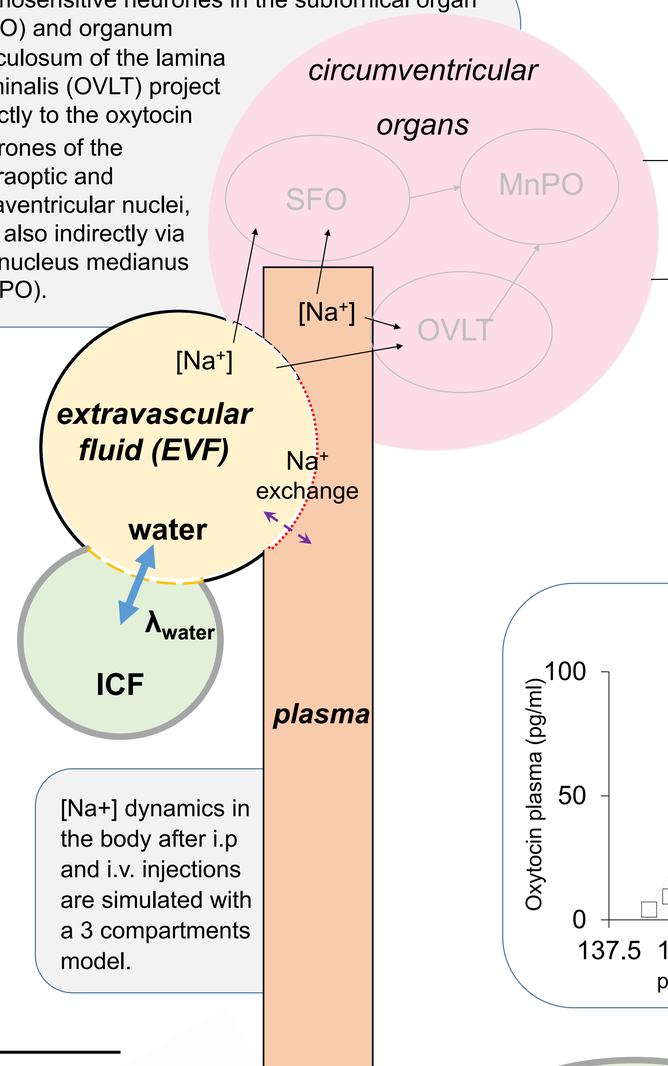
In rodents and in some but not all other mammals, oxytocin responds to plasma osmotic pressure and blood volume to regulate sodium excretion at the kidneys. Oxytocin neurones respond to increases in plasma osmotic pressure partly as a result of intrinsic osmosensitivity, but also as a result of increased afferent input arising directly and indirectly from osmoreceptors in other forebrain regions. Experiments generate an osmotic challenge by injecting or infusing NaCl.

Here we present a previous computational model integrated with a new one that simulates the [Na+] dynamics in the body. To test the full model we have matched different experimental data from rats under hypertonic and hypovolemic challenges.



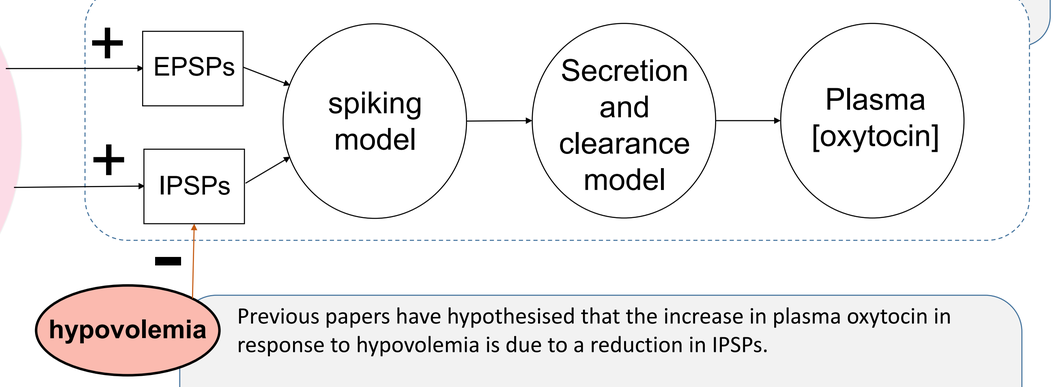
A I.v. NaCl infusion produces a linear increase in the oxytocin neurones spike rate. We can simulate that by making the firing rate dependant on the EVF [Na+] (top). The result in spike activity (middle) and oxytocin plasma match the *in vivo* data closely.

Osmosensitive neurones in the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) project directly to the oxytocin neurones of the supraoptic and paraventricular nuclei, and also indirectly via the nucleus medianus (MnPO).



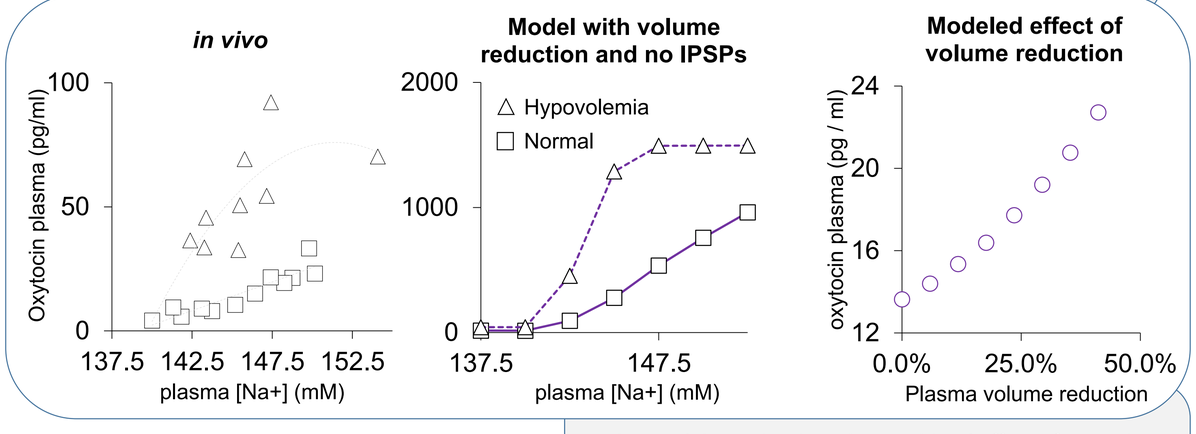
[Na+] dynamics in the body after i.p and i.v. injections are simulated with a 3 compartments model.

Our previous model links oxytocin neurone properties, including excitatory and inhibitory post synaptic potentials (EPSPs and IPSPs) to spike activity, spike activity to secretion, and secretion to the dynamics of oxytocin in plasma.

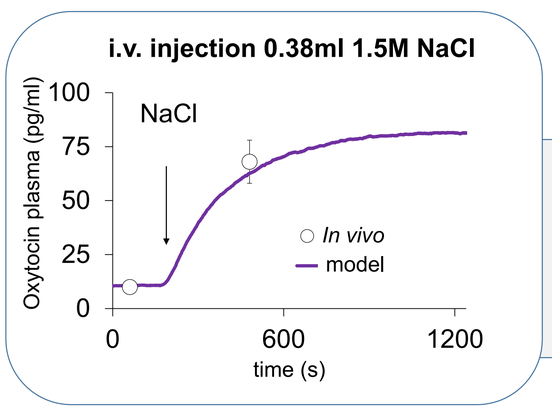


Previous papers have hypothesised that the increase in plasma oxytocin in response to hypovolemia is due to a reduction in IPSPs.

However, our model predicts that an increment in plasma oxytocin is possible in hypovolemic conditions (less plasma volume and more EVF volume) without a change in the oxytocin neurones activity.

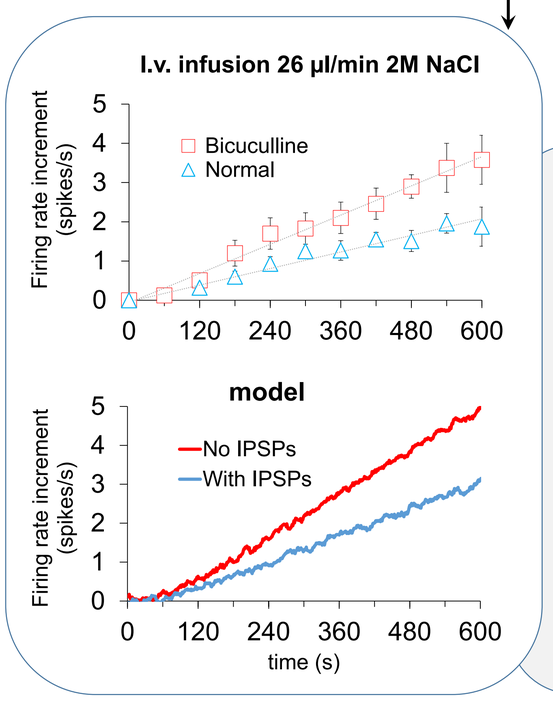


The model can simulate the combined effect of osmotic pressure and hypovolemia (on the left, experimental data and on the middle the modelled data). The model predicts that part of the effect is due to the volume exchange between plasma and EVF.



injection

Matching independent data when NaCl is injected i.v. instead of infused

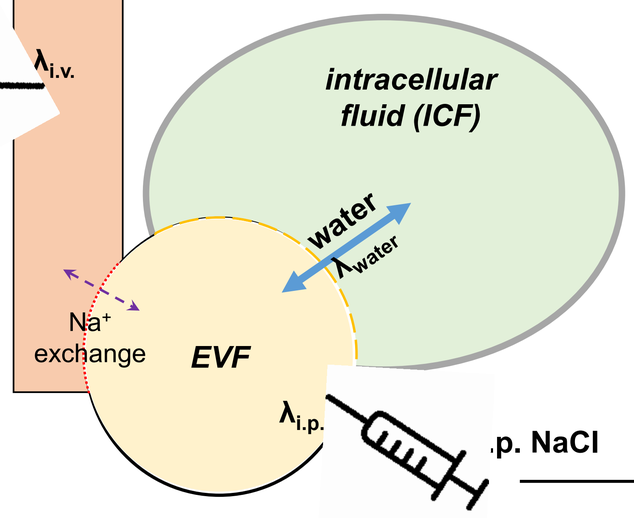


Infusion & bicuculline

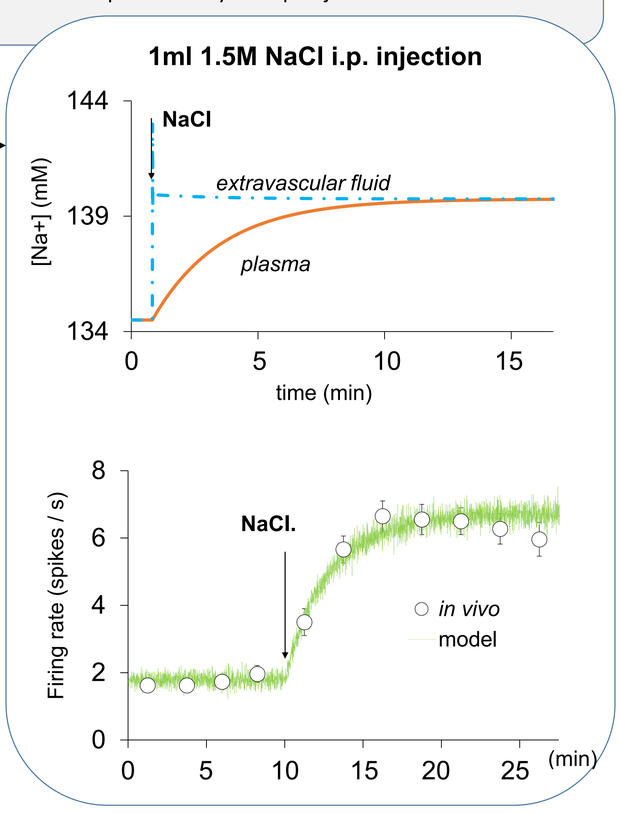
Osmotic stimuli result in increases in both GABA and glutamate release in the supraoptic nucleus. (blue triangles are in vivo data and the blue line shows our model response)

Injecting bicuculline in the SON blocks GABAergic neurones, supresses the IPSPs (red squares).

We can simulate the response of oxytocin neurons to bicuculline by removing the IPSPs while keeping the same amount of EPSPs (red line).



NaCl i.p. injections take more time to be detected at the circumventricular organs. We can model that effect by making the firing rate dependant of the plasma [Na+], which follows the changes in the EVF produced by the i.p. injection.



The previously published model of the oxytocin system appears to be fully quantitatively predictive.

From spike activity, the changes in plasma oxytocin concentration can be reliably inferred and vice versa.

The model can give predictive insight into features of physiological behaviour, in particular by revealing a likely mechanism by which hypovolemia alters the gain of osmoresponsiveness.

References

Maícas Royo J, Brown CH, Leng G & MacGregor DJ (2016). Oxytocin Neurones: Intrinsic Mechanisms Governing the Regularity of Spiking Activity. *J Neuroendocrinol* **28.**

Maícas-Royo J, Leng G & MacGregor DJ (2018). A Predictive, Quantitative Model of Spiking Activity and Stimulus-Secretion Coupling in Oxytocin Neurons. *Endocrinology* **159,** 1433–1452.

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