A Mechanism for Circadian Pulsatile Prolactin Secretion Triggered by a Brief Mating Stimulus

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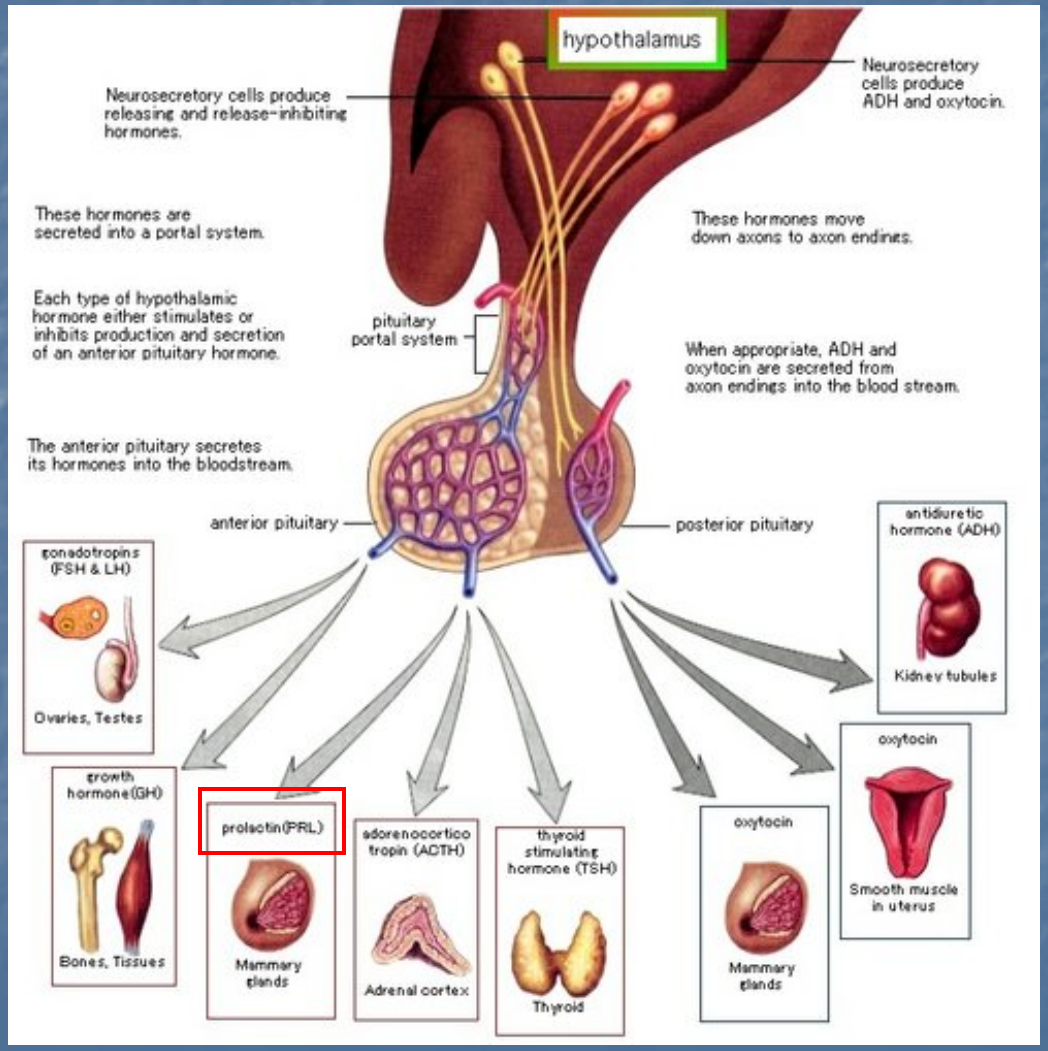
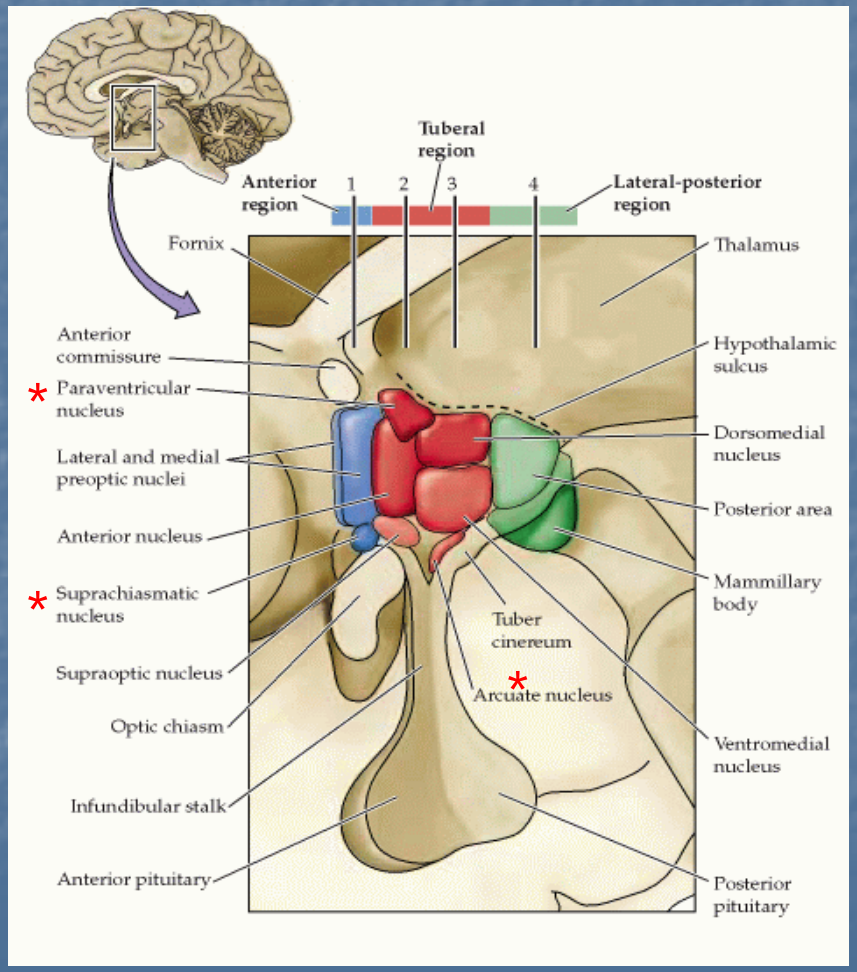
The Neuroendocrine System



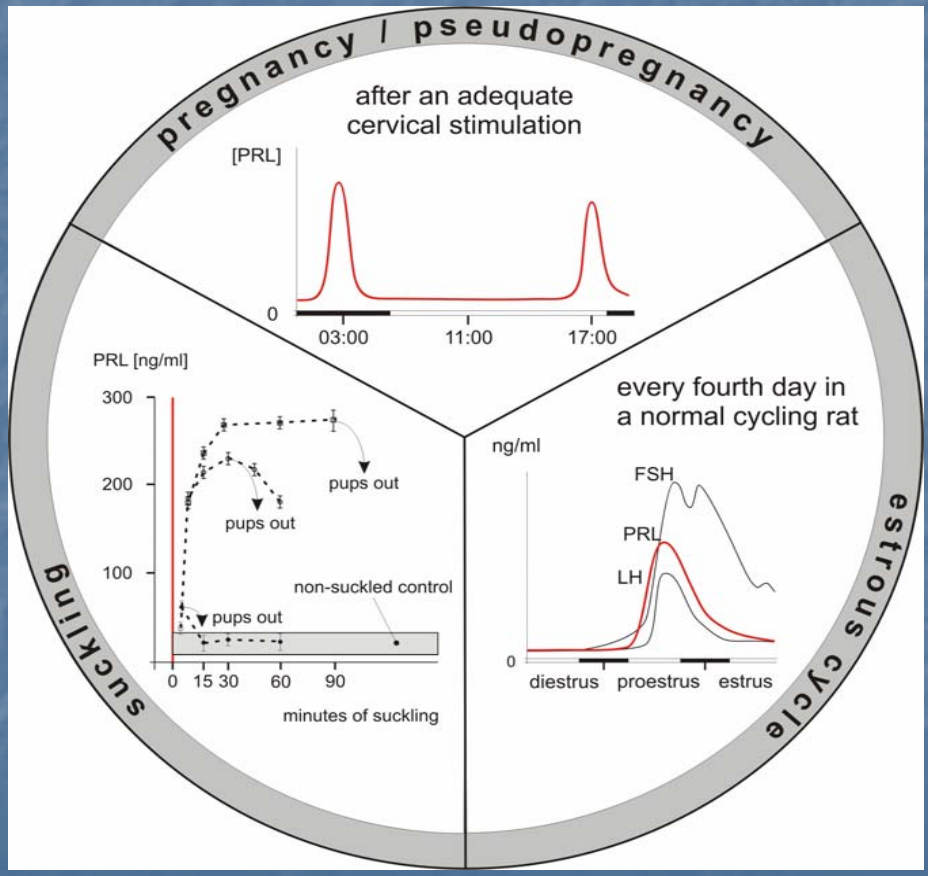
Nuclei of the Hypothalamus



Prolactin Release from Lactotrophs

- The hormone prolactin (PRL) has over 100 functions. Two important functions are the production of milk and parental behavior.

- The pattern of PRL release depends on the state of the animal and external stimuli.



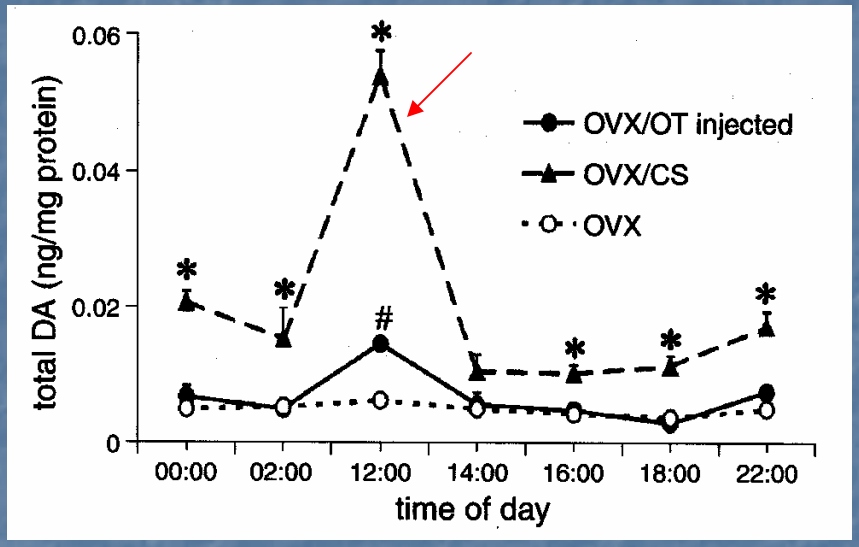
PRL release patterns in female rats

Key Experiment: Cervical stimulation (CS) of ovariectomized rats produces a circadian PRL rhythm that is similar to that produced by mating (Smith et al., 1975)

What is the mechanism for the CS-induced Prolactin (PRL) rhythm?

A Brief History of our Theories and Experiments

Hint: Dopamine Levels are Also Oscillatory



Egli et al., AJP, 290:E566, 2006

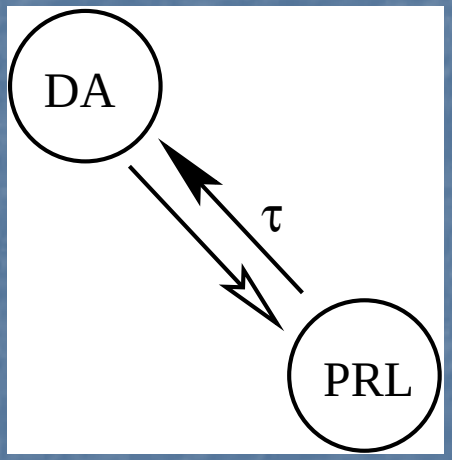
Dopamine (DA) content in the anterior lobe of the pituitary following cervical stimulation (CS) in ovariectomized (OVX) rats. There is a circadian rhythm in DA that peaks at around noon.

DA-PRL Feedback Interactions

DA inhibits PRL release from lactotrophs. This negative action is rapid.

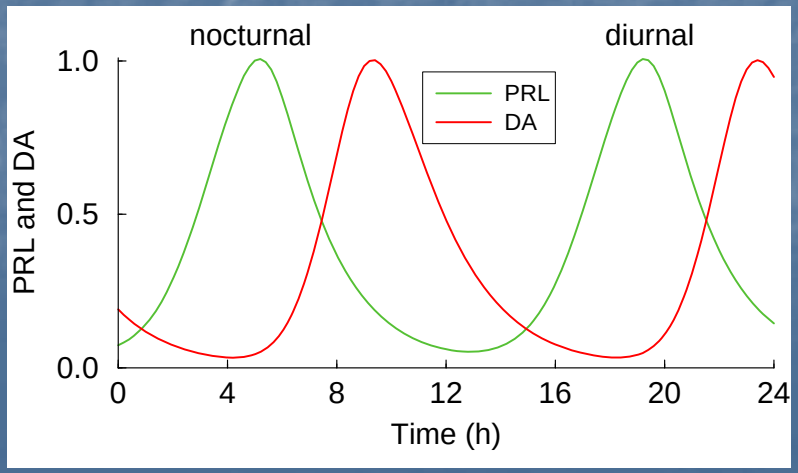
PRL stimulates DA neurons. This positive feedback is slow or delayed.

Hypothesis (2006): DA-PRL Circuit Produces the Rhythm



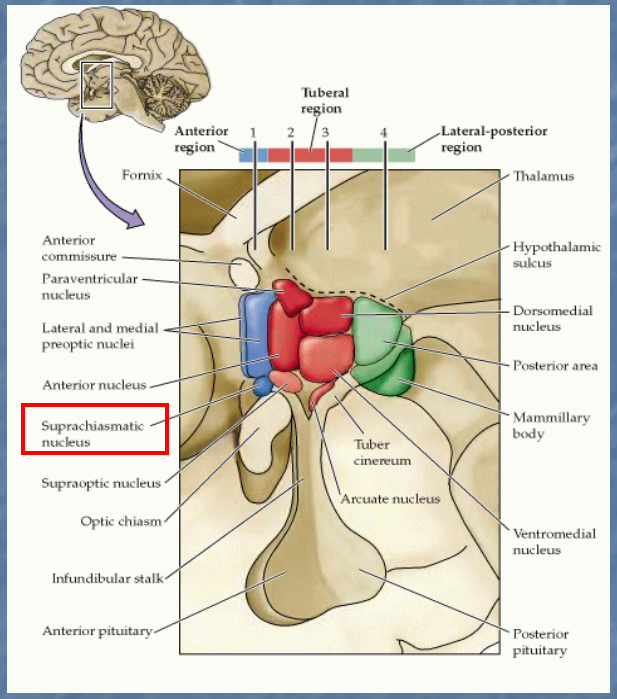
$$\frac{dPRL}{dt} = \frac{T_p}{1 + k_d DA^2} - qPRL$$

$$\frac{dDA}{dt} = T_d + k_p PRL_\tau^2 - qDA$$

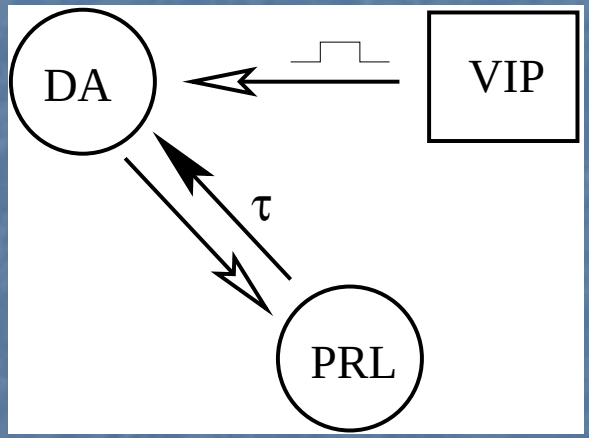


$\tau = 3$ hours

SCN Provides Circadian Input



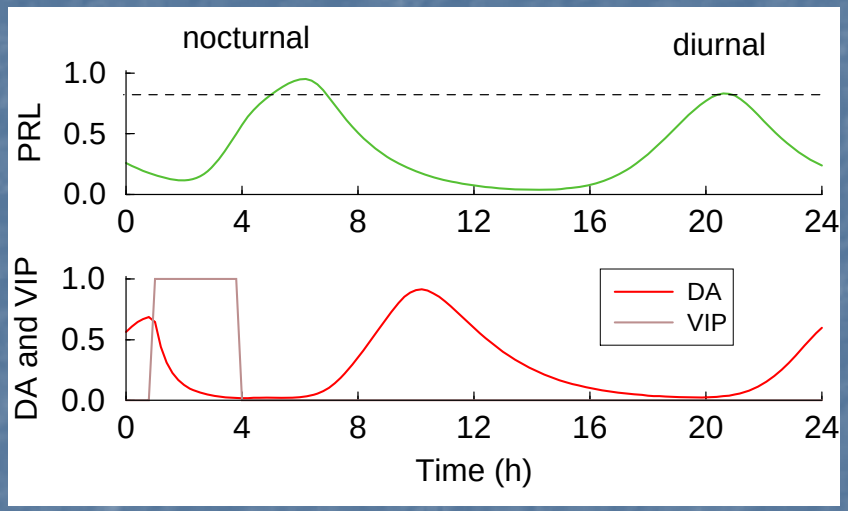
Neurons of the **suprachiasmatic nucleus (SCN)** that release vasoactive intestinal polypeptide (VIP) are most active early in the morning. They are inhibitory to DA neurons.



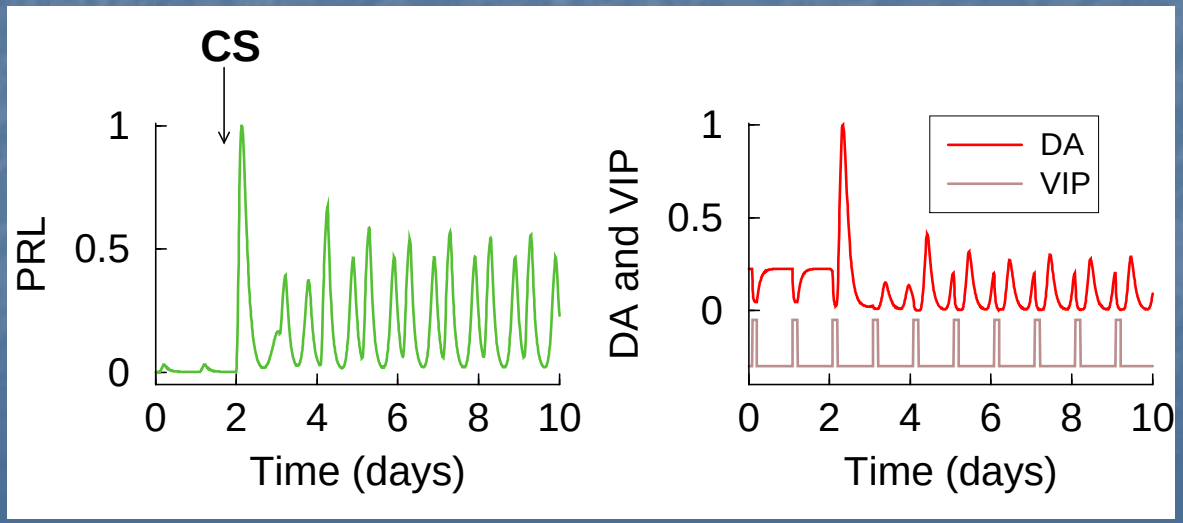
$$\frac{dDA}{dt} = T_d + k_p PRL_\tau^2 - qDA - r_v VIP \cdot DA$$

Rhythm Generator is Complete (2006)

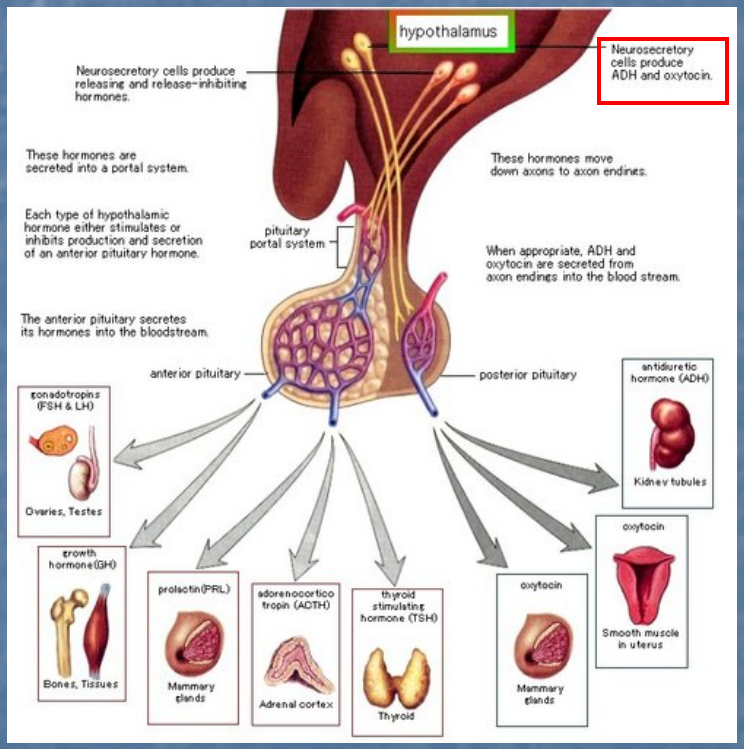
Rhythm during a single day



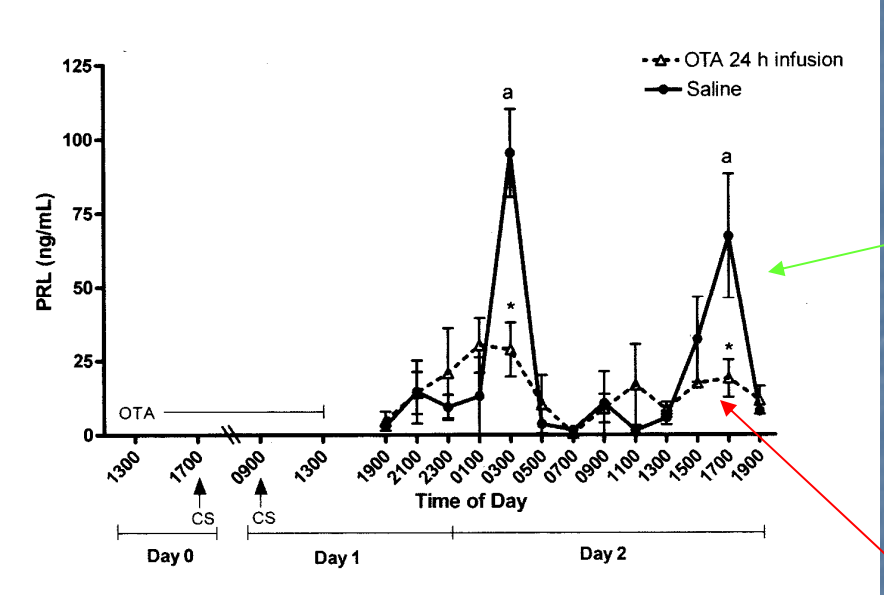
Rhythm during 10 days



What About Oxytocin (OT)?



An OT Antagonist Blocks the PRL Rhythm (2007)



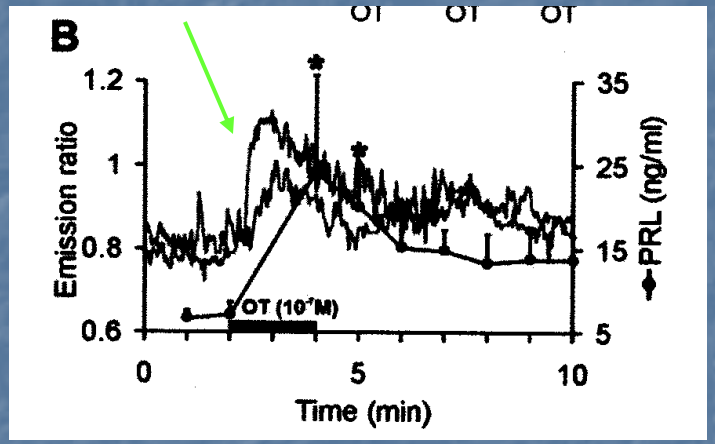
control

OT antagonist

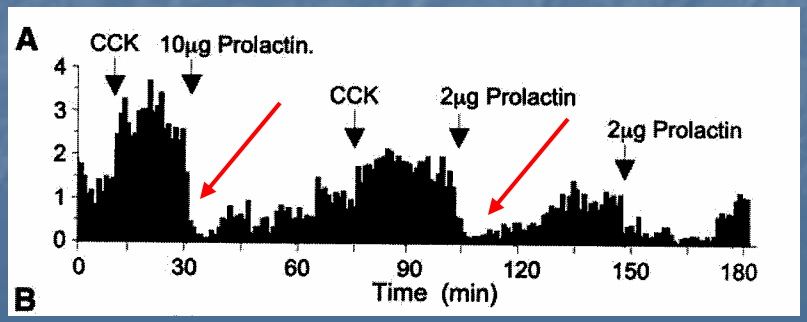
(McKee et al., Endocrinology, 2007)

Must Include OT Effects in the Model

OT stimulates PRL release *in vitro* (Egli et al., Endocrinology, 2004)

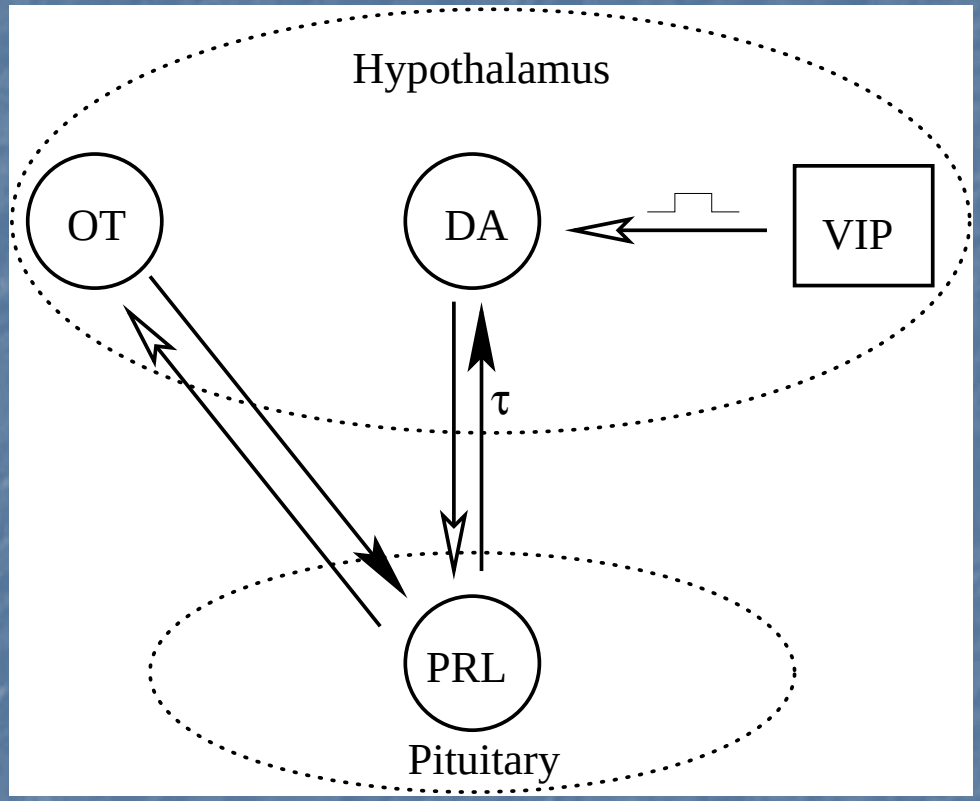


Firing rate



PRL inhibits OT neurons in the paraventricular nucleus (PVN) (Kokay et al., Am. J. Physiol., 2006)

The Model with OT-PRL Interactions (2007)

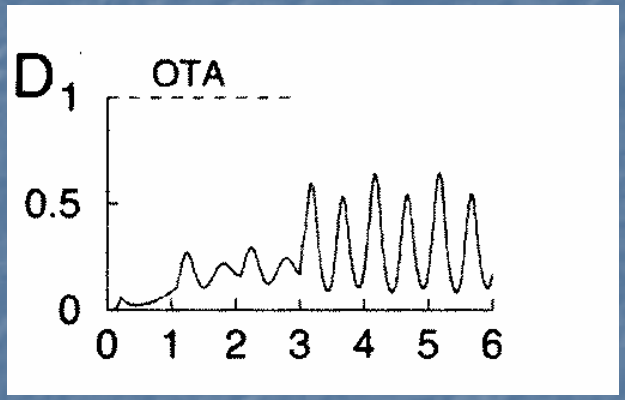


$$\frac{dPRL}{dt} = \frac{T_p + \nu_O OT}{1 + k_d DA^2} - qPRL$$

$$\frac{dOT}{dt} = \frac{T_O}{1 + k_O PRL^2} - qOT$$

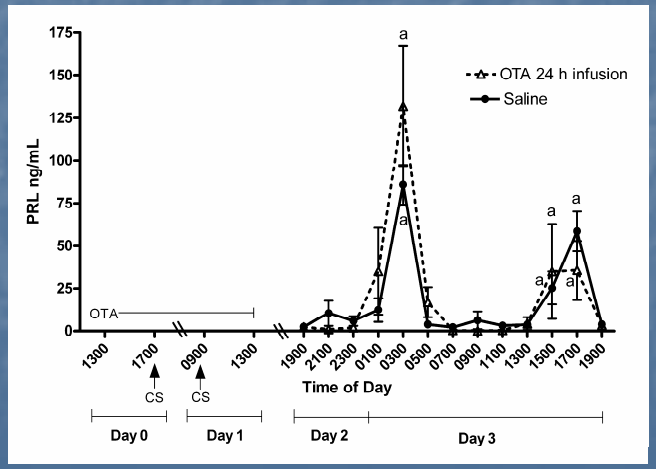
Simulation and Prediction

Simulation



Prediction: The PRL rhythm will return when the OT antagonist leaves the system. That is, OT at the lactotroph is not responsible for triggering the rhythm, just facilitating its expression.

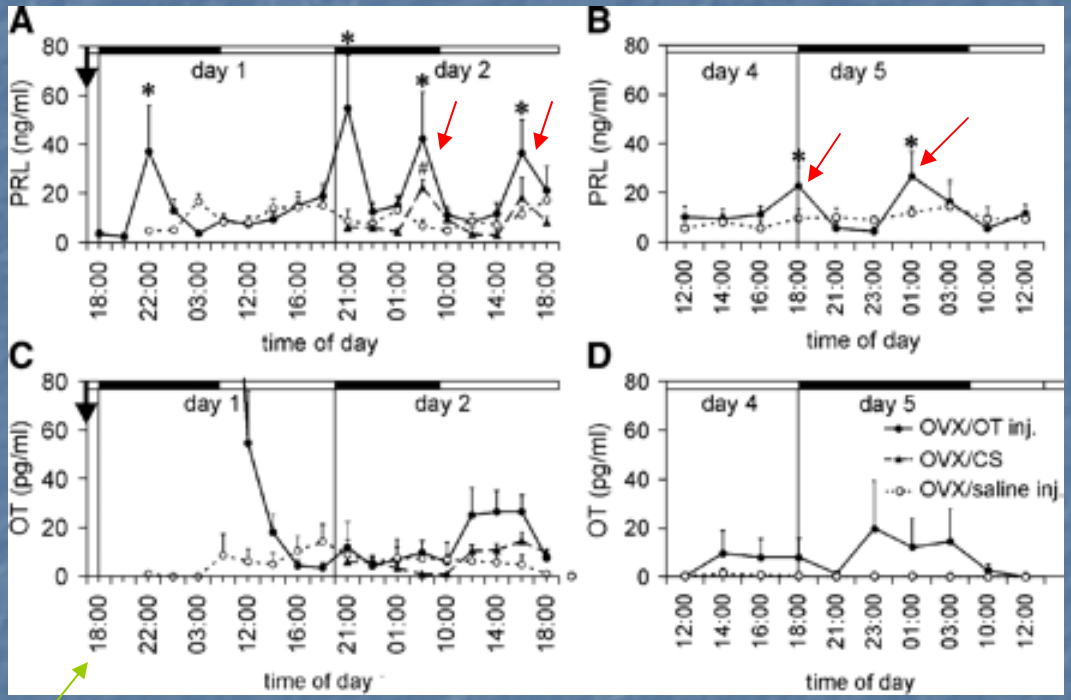
As predicted, the PRL rhythm comes back once the antagonist clears the system.



(McKee et al., Endocrinology, 2007)

How is the PRL Rhythm Initiated?

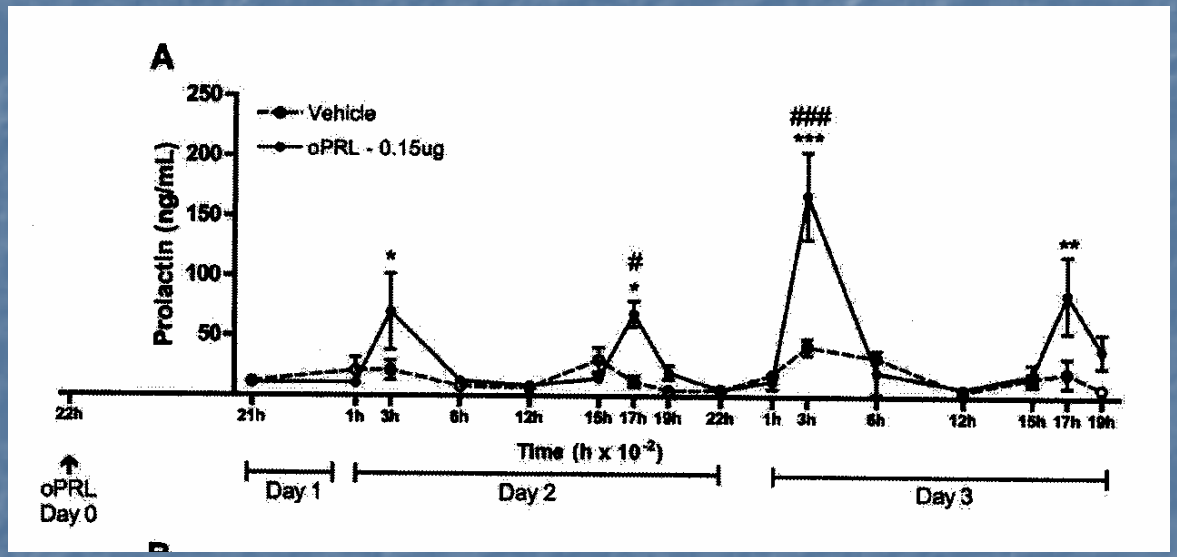
Injection of Oxytocin (OT) can Initiate the PRL Rhythm



OT injected

Egli et al., AJP, 2006

Injection of Ovine PRL Also Triggers the Rhythm (2009)



Helena et al., Endocrinology, 2009

Question: What do cervical stimulation, oxytocin, and prolactin have in common?

Answer: I wish I knew. Stay tuned...

Thank You!!