The Emerging Roles of Oxytocin in Rhythmic Prolactin Release

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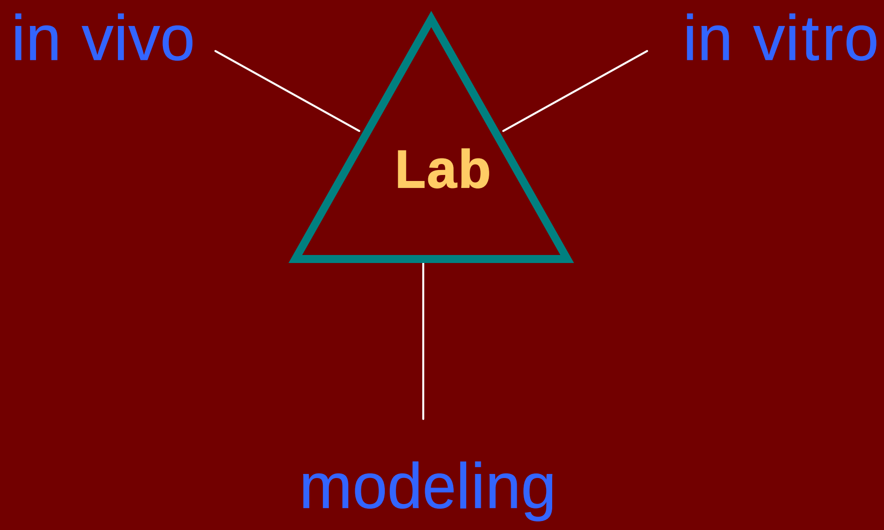
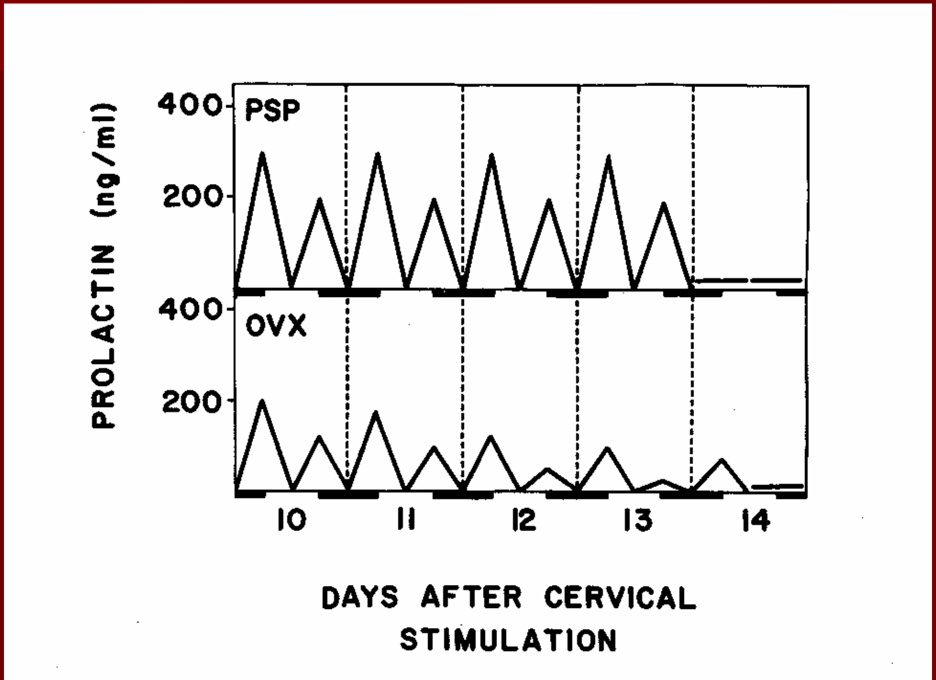
Types of Studies Performed in the Lab



Circadian Prolactin Rhythm in Female Rats

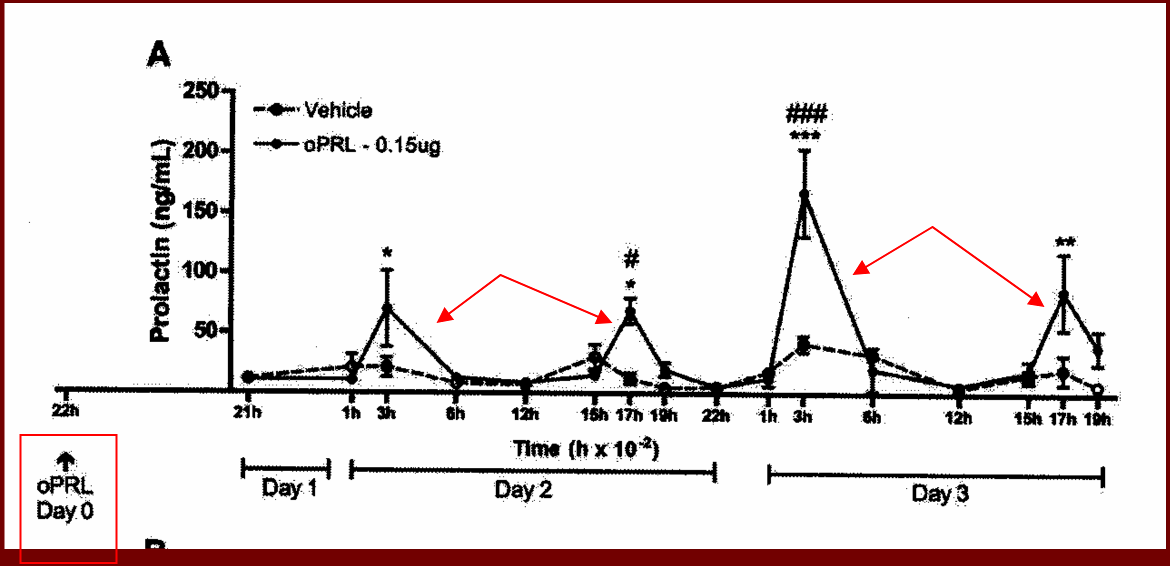


PSP – Pseudopregnancy, rhythm induced by mating

OVX – ovaries removed, rhythm induced by artificial cervical stimulation (CS). Our in vivo work is typically done with OVX rats.

Central Injection of Prolactin Itself Can Trigger the Prolactin Rhythm

Intracerebroventricular (icv) injection of ovine prolactin



OVX rats

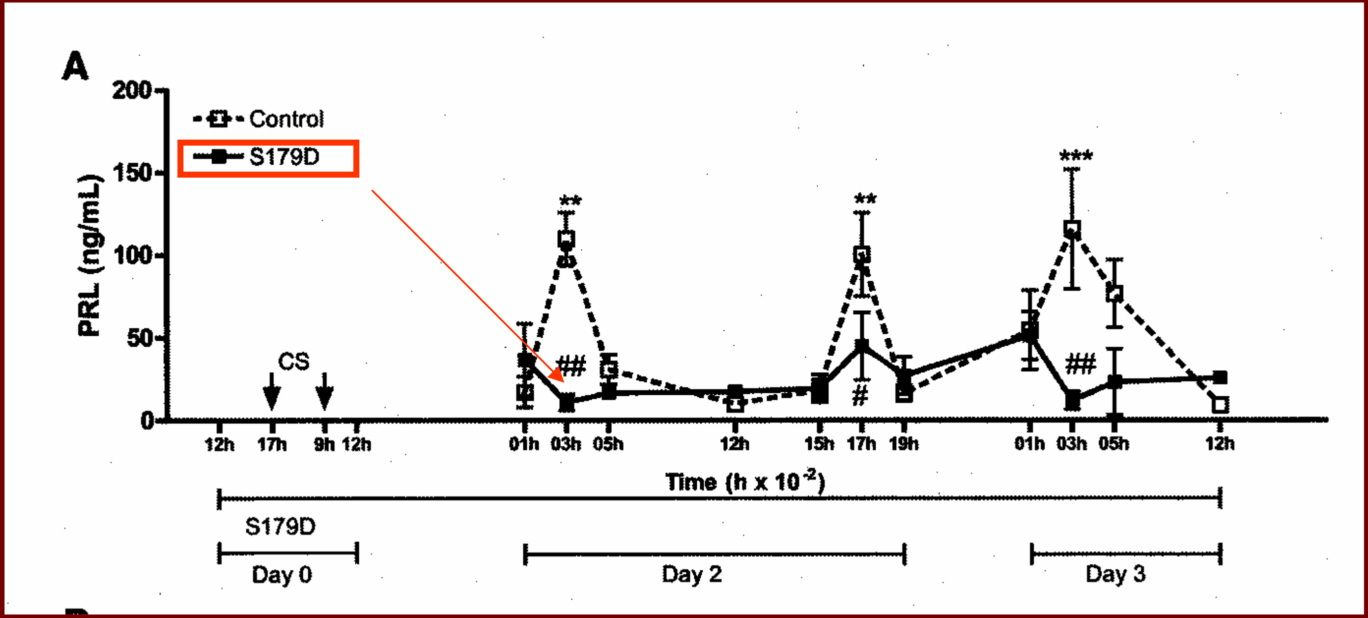
Helena et al., Endocrinology, 150:3245, 2009

oPRL – ovine prolactin

Systemic administration of prolactin also works, but the required concentration is much higher

Central Blockade of Prolactin Receptors Inhibits the CS-Induced Prolactin Rhythm

Icv infusion of prolactin antagonist

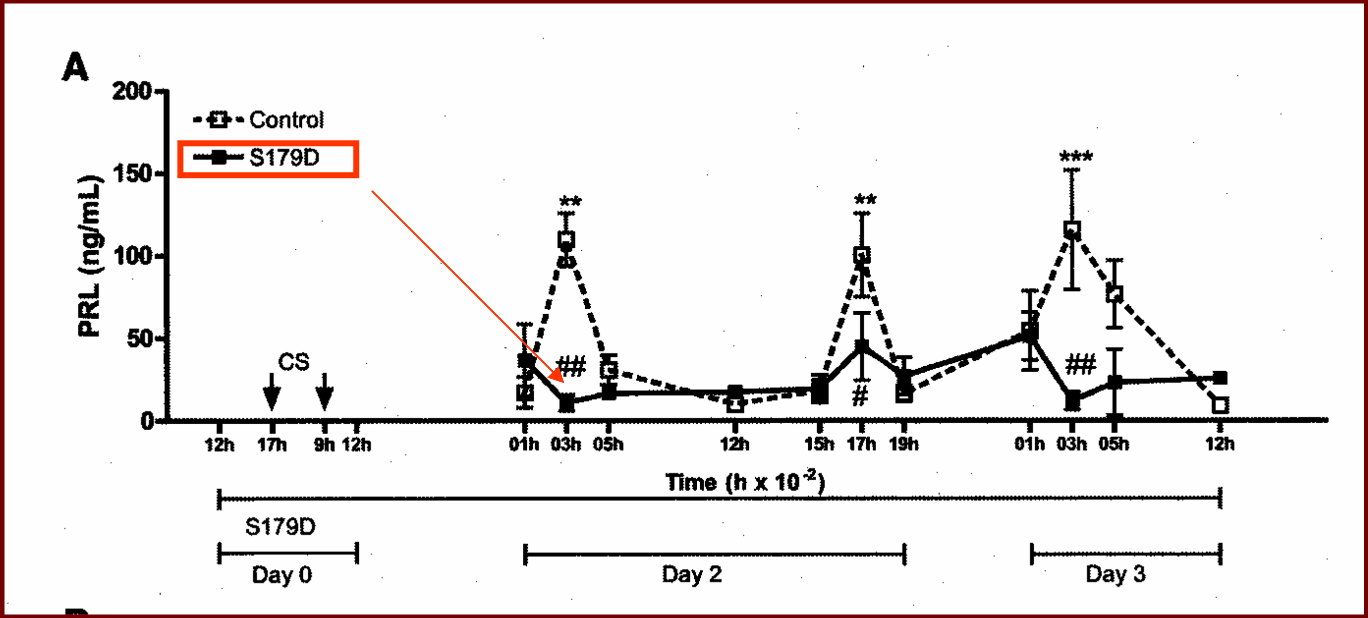


Helena et al., Endocrinology, 150:3245, 2009

S179D – Prolactin receptor antagonist

Central Blockade of Prolactin Receptors Inhibits the CS-Induced Prolactin Rhythm

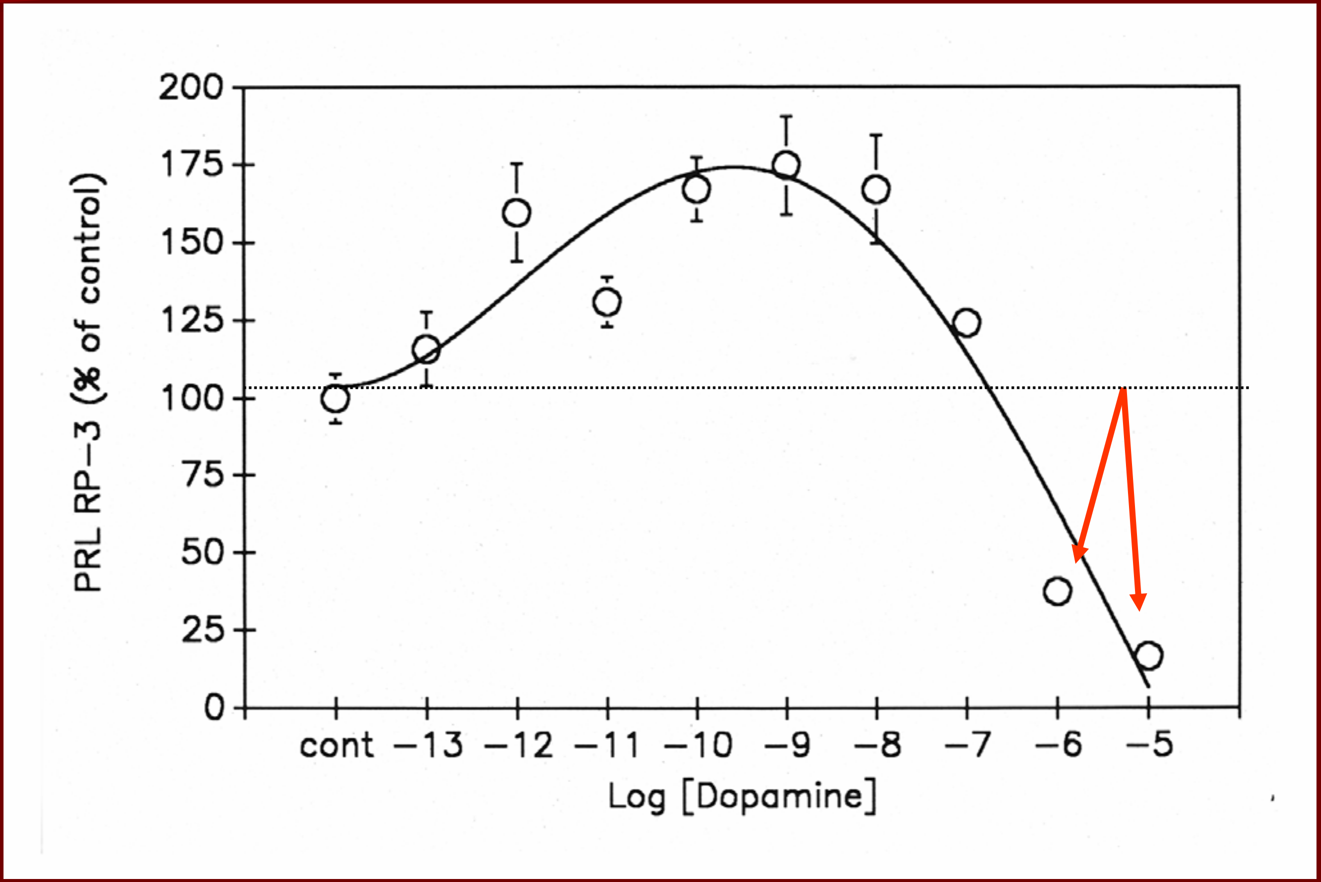
Icv infusion of prolactin antagonist



Central prolactin feedback is necessary for the rhythm!

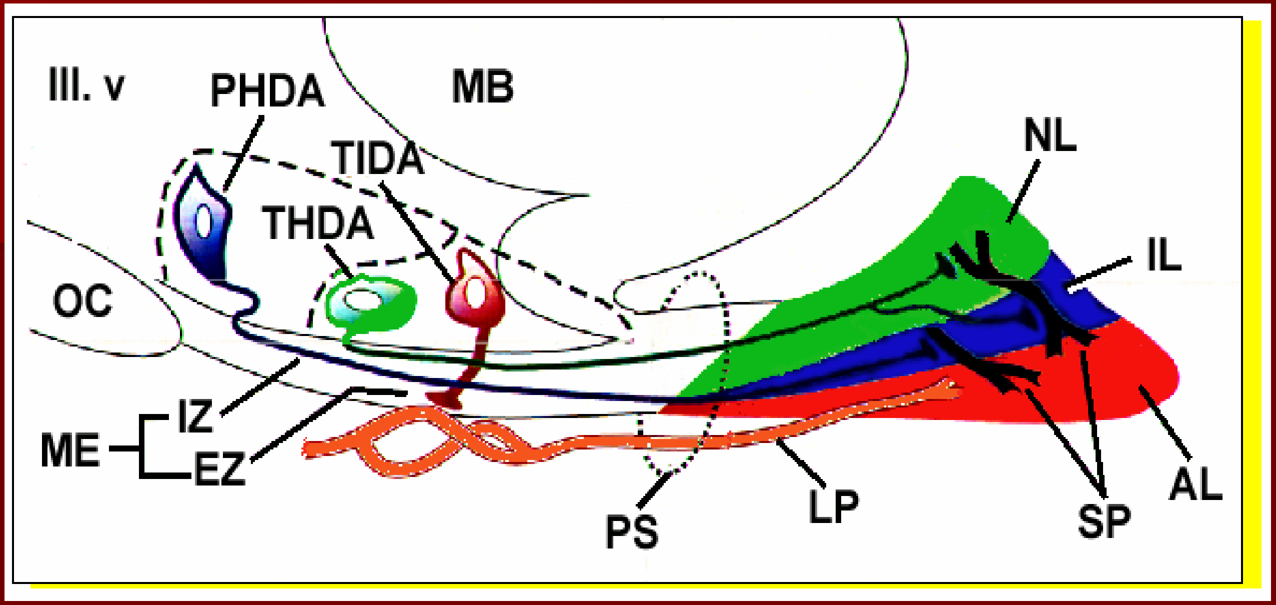
What is the Mechanism for this Rhythm?

Dopamine is the Physiological Inhibitor of Prolactin Release



Arey et al., Proc. Soc. Exp. Biol. Med., 203:60, 1993

Dopamine From 3 Sources



Tuberoinfundibular (TIDA):
Dorsomedial ARN → Median eminence

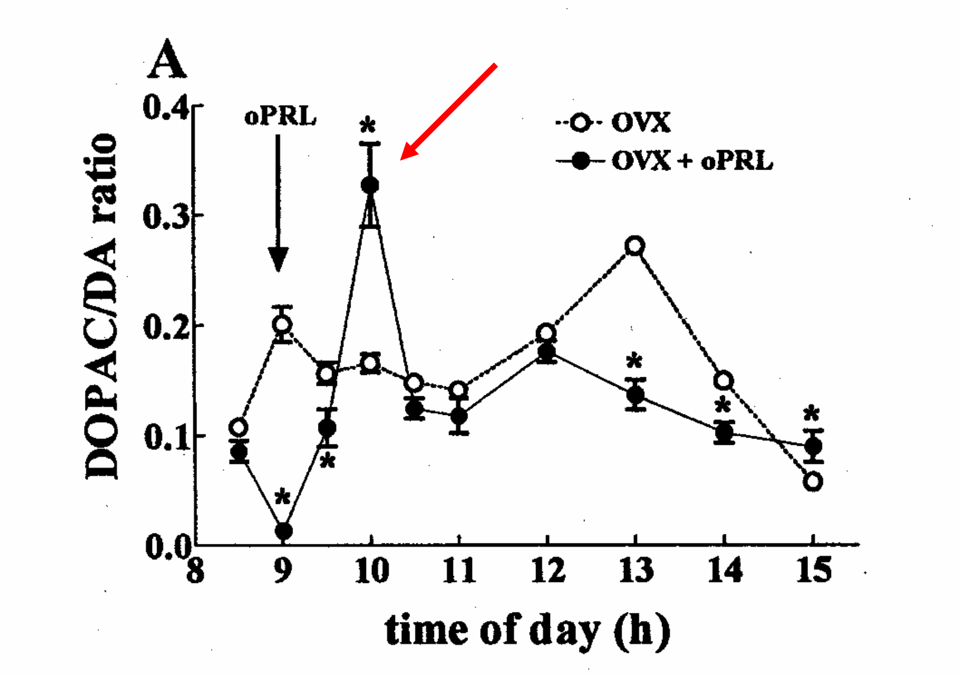
Tuberohypophysial (THDA):
Rostral ARN → Neural and intermediate lobes

Periventricular hypophysial (PHDA):
PeVN → Intermediate lobe

Prolactin Stimulates Neuroendocrine Dopamine Secretion

In median eminence

Also true for neural and intermediate lobes

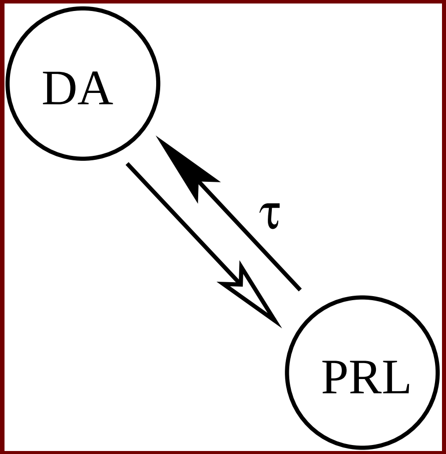


Systemic ovine prolactin injection

DeMaria et al., Brain Res. 837:236, 1999

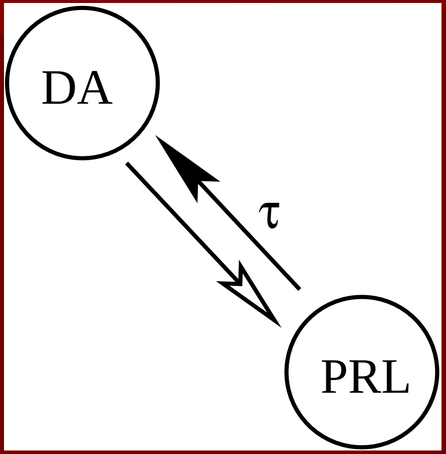
DOPAC – the major metabolite of dopamine
oPRL – ovine prolactin

Hypothesis: The Dopamine-Prolactin Circuit Produces the Rhythm



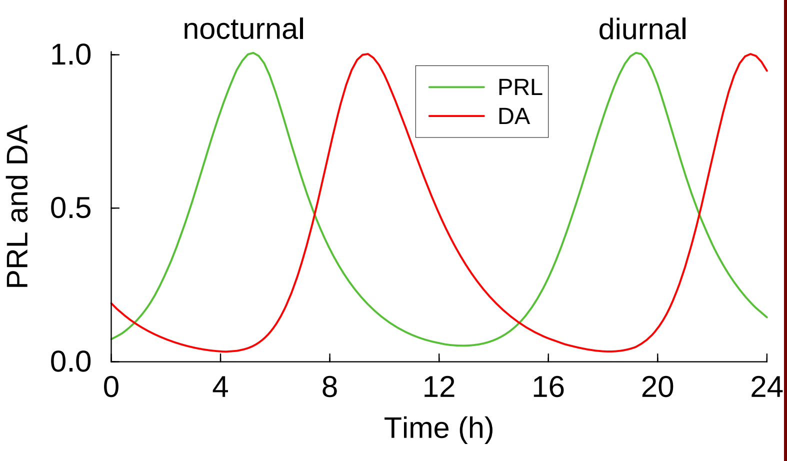
This can happen only if the positive feedback of prolactin onto dopamine neurons is delayed. There is evidence for such a delay
(Ma et al., Endocrinology, 146:93, 2005;
DeMaria et al., Brain Res., 837:236, 1999)

Our Approach: Build a Math Model



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

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

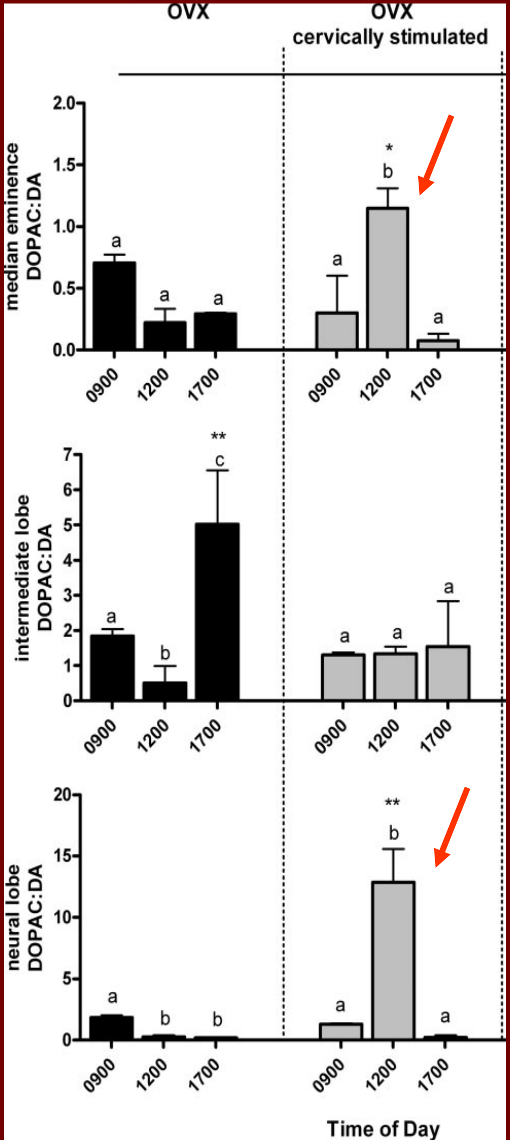


$\tau = 3$ hours

Bertram et al.,
AJP, 290:E573, 2006

Prediction: Dopamine Levels Should Be Out of Phase with Prolactin Levels

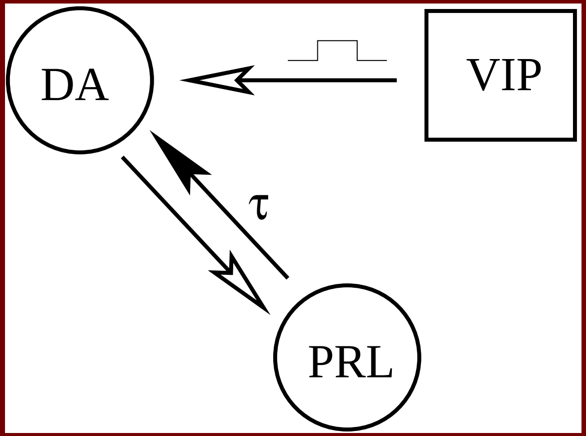
Dopamine secretion into the median eminence and the neural lobe peaks at noon, between the prolactin surges



McKee et al., Endocrinology, 148:4649, 2007

Input from the Suprachiasmatic Nucleus

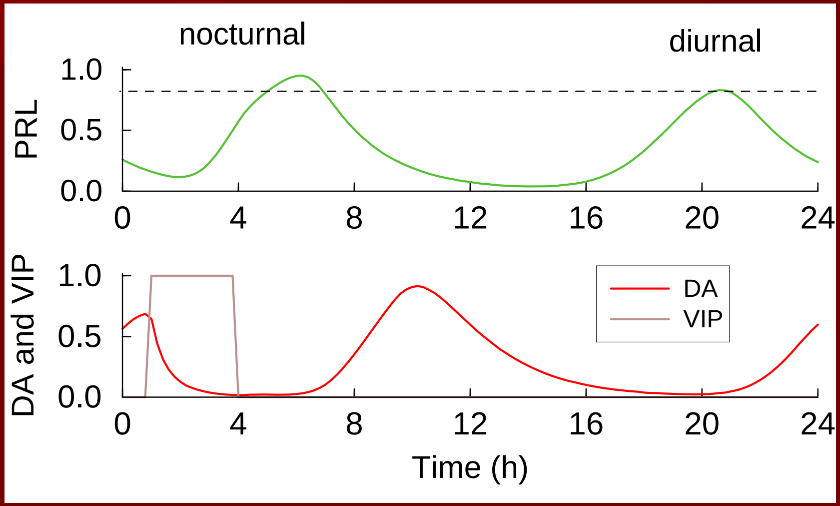
Neurons of the suprachiasmatic nucleus (SCN) that project to the arcuate nucleus and release vasoactive intestinal polypeptide (VIP) are most active early in the morning. They are inhibitory to DA neurons.



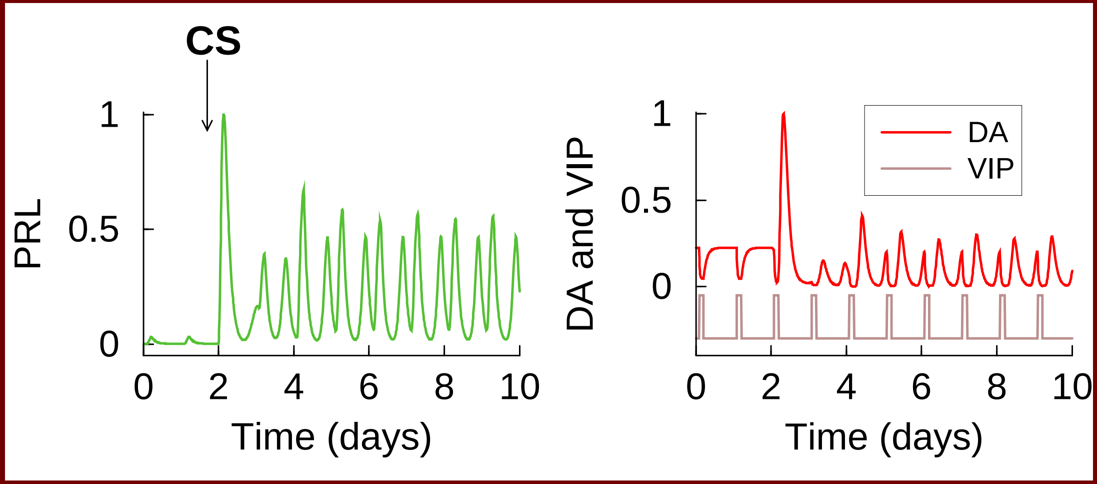
$$\frac{d\,DA}{dt} = T_d + k_p PRL_\tau^2 - qDA - r_v VIP \cdot DA$$

Improved Rhythm Generator

Rhythm during one day

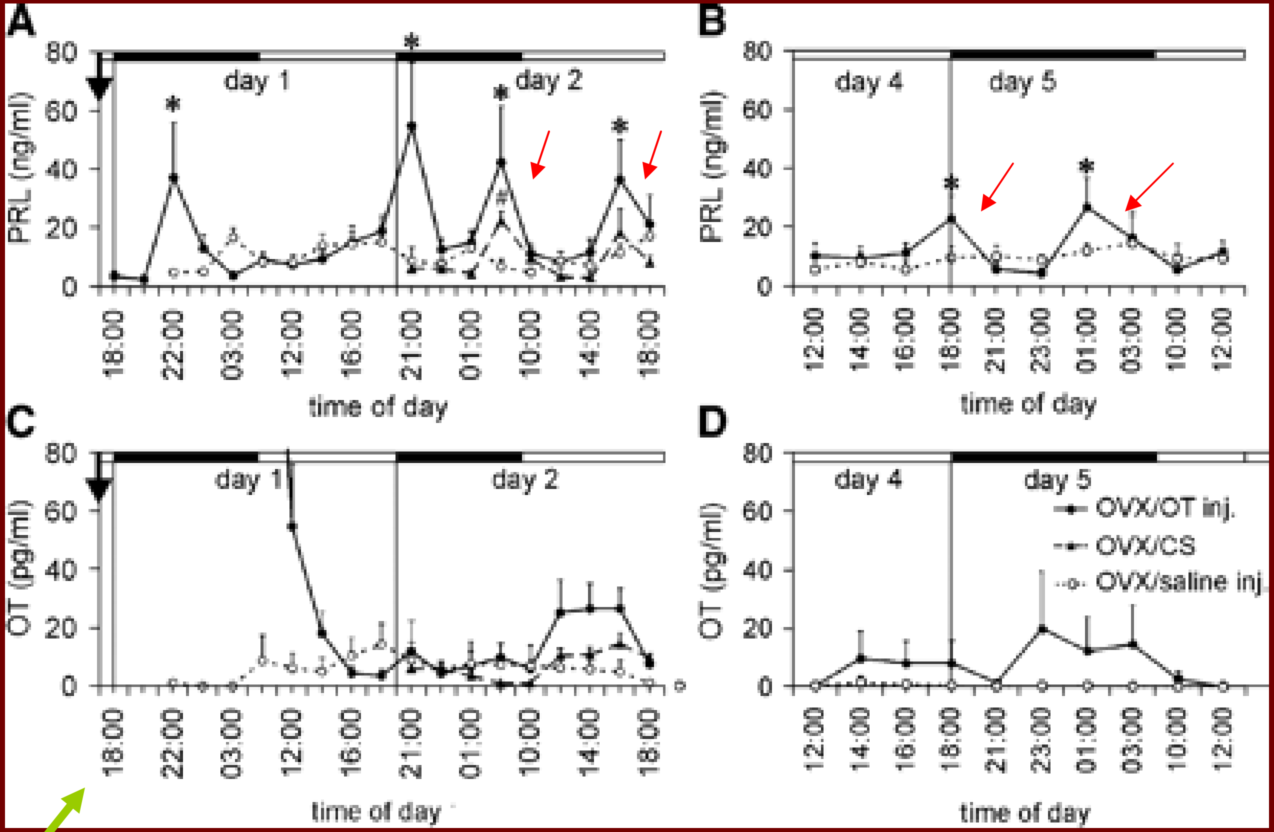


Rhythm during 10 days



CS simulated by partial inhibition of dopamine neurons

Oxytocin Injection Can Initiate the Prolactin Rhythm



OT injected

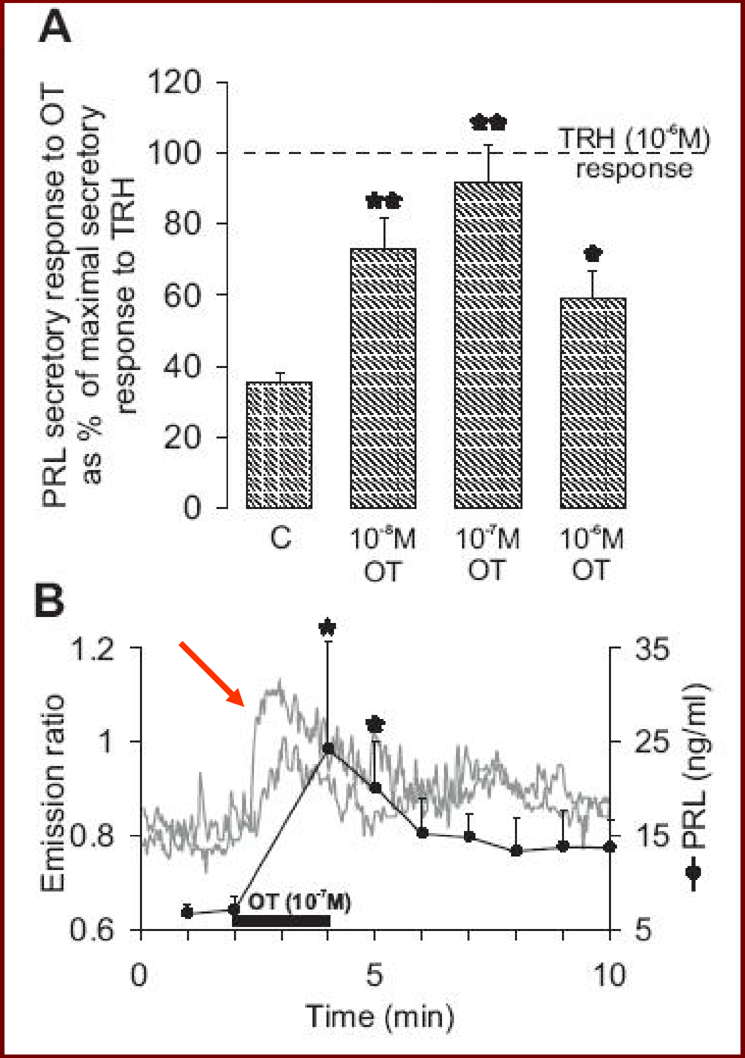
Egli et al., AJP 290:E566, 2006

What Role Does Oxytocin Play in the Prolactin Rhythm?

Oxytocin Stimulates Prolactin Secretion From Lactotrophs *in vitro* Through a Calcium-Linked Mechanism

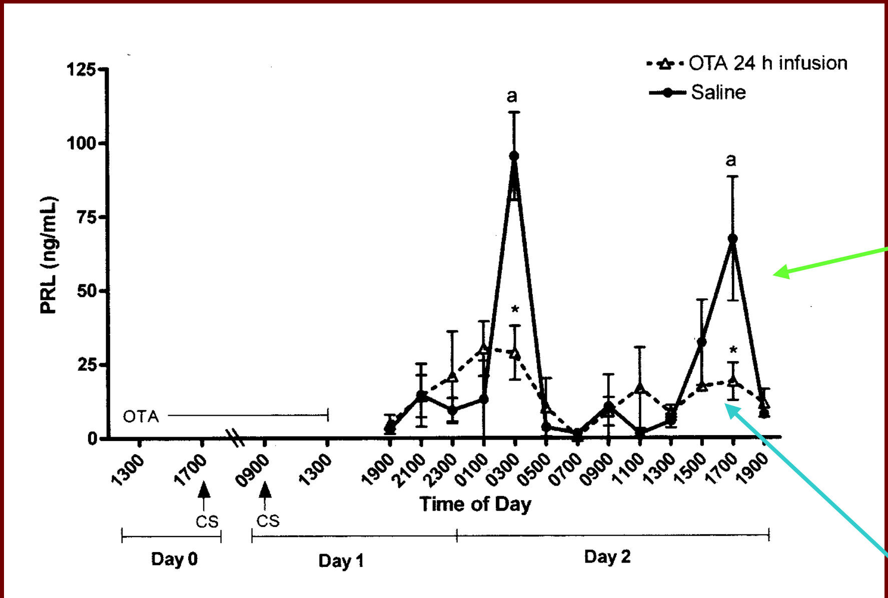
Secretion

Intracellular calcium



Egli et al., Endocrinology 145:3386, 2004

An Oxytocin Antagonist Can Prevent the CS-Induced Prolactin Rhythm



control

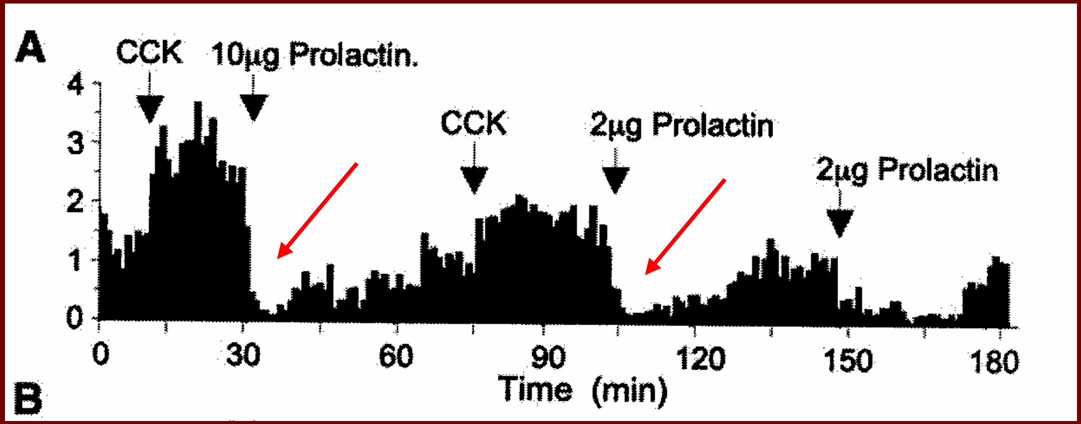
OT antagonist

(McKee et al., Endocrinology, 148:4649, 2007)

CS – cervical stimulation
OTA – oxytocin antagonist

Prolactin Feeds Back Onto and Inhibits Oxytocin Neurons of the Supraoptic Nucleus (SON) and Perhaps the Paraventricular Nucleus (PVN)

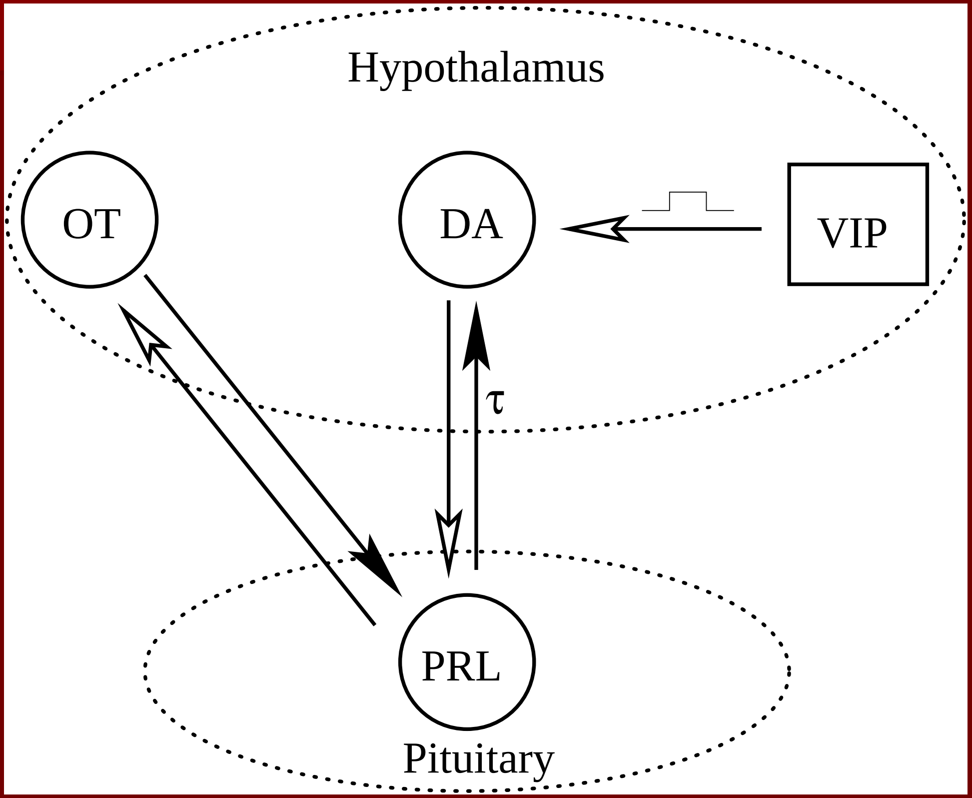
Electrical firing rate with extracellular recording from the SON



Kokay et al., AJP 290:R1216, 2006

CCK – stimulating agent

Model with Oxytocin Interactions



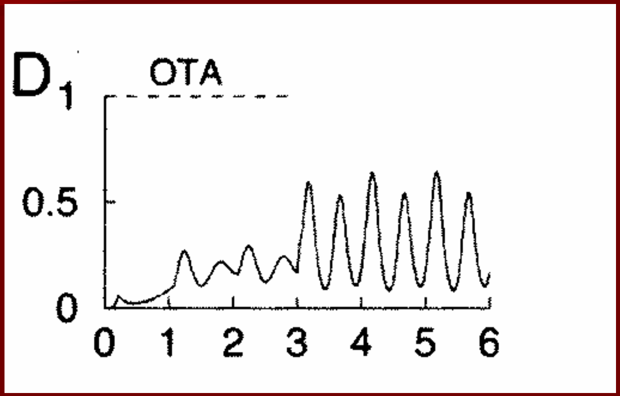
$$\frac{dPRL}{dt} = \frac{T_p + v_O OT}{1 + k_d DA^2} - qPRL$$

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

Simulation and Prediction

Simulation

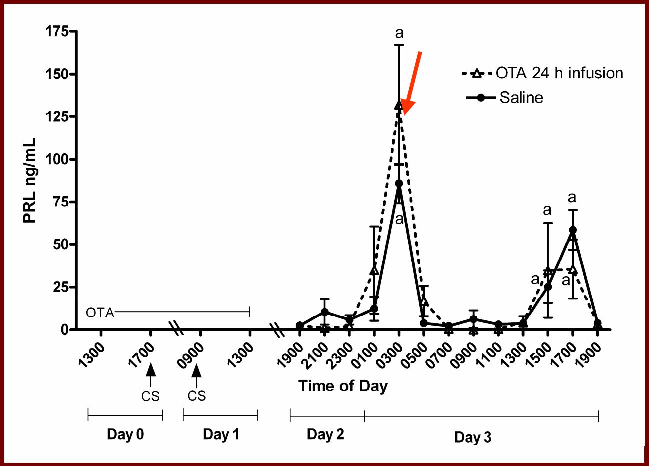
PRL



Time (days)

Prediction: The PRL rhythm will return when the OT antagonist leaves the system. That is, OT at the lactotroph is required for the expression of the rhythm, but not for triggering the rhythm.

As predicted, the prolactin rhythm comes back once the antagonist clears the system (day 2 – no rhythm; day 3 – rhythm present)



(McKee et al., Endocrinology, 148:4649, 2007)

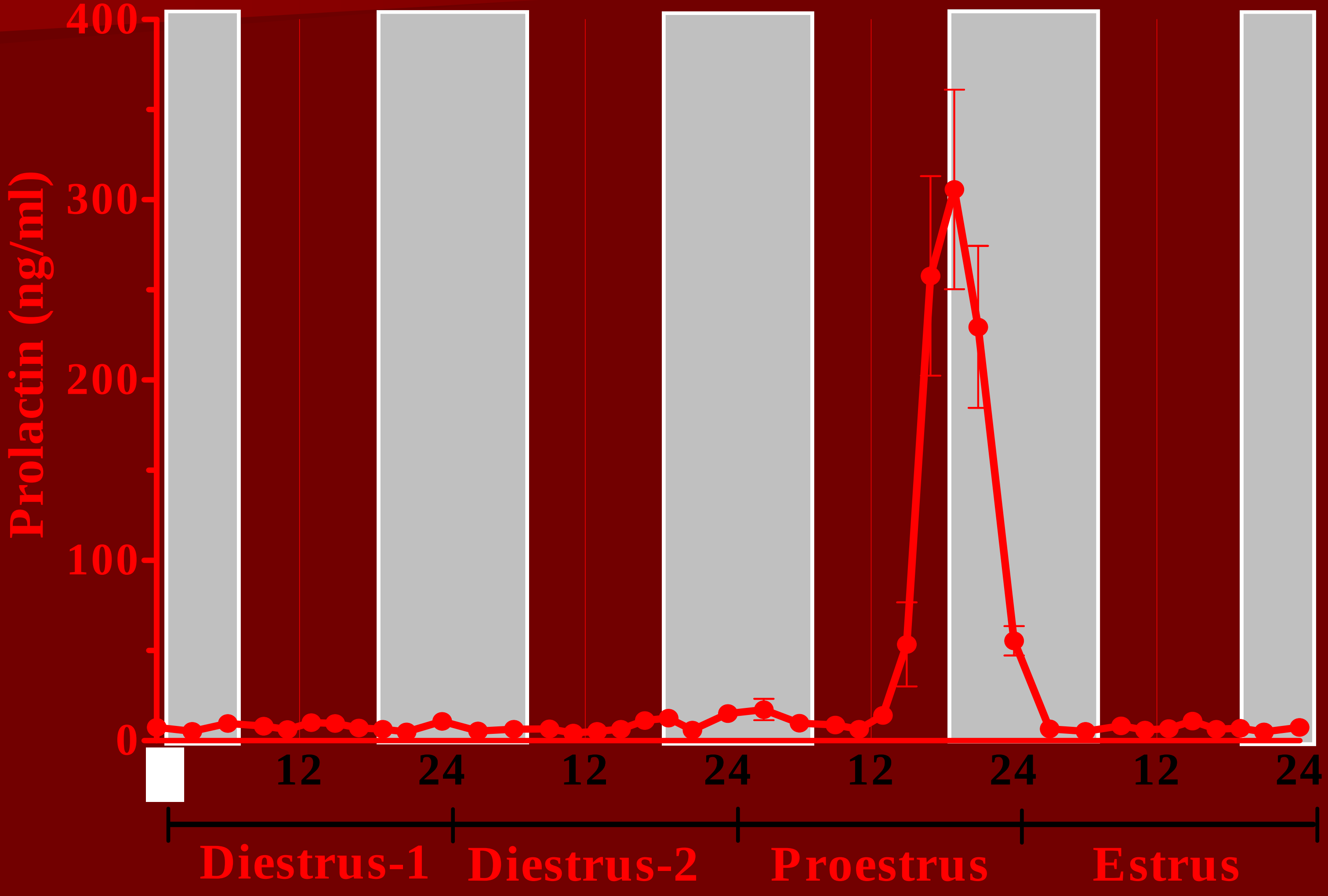
Conclusions: Part 1

1. The prolactin rhythm is likely due to interactions between dopamine neurons and lactotrophs.

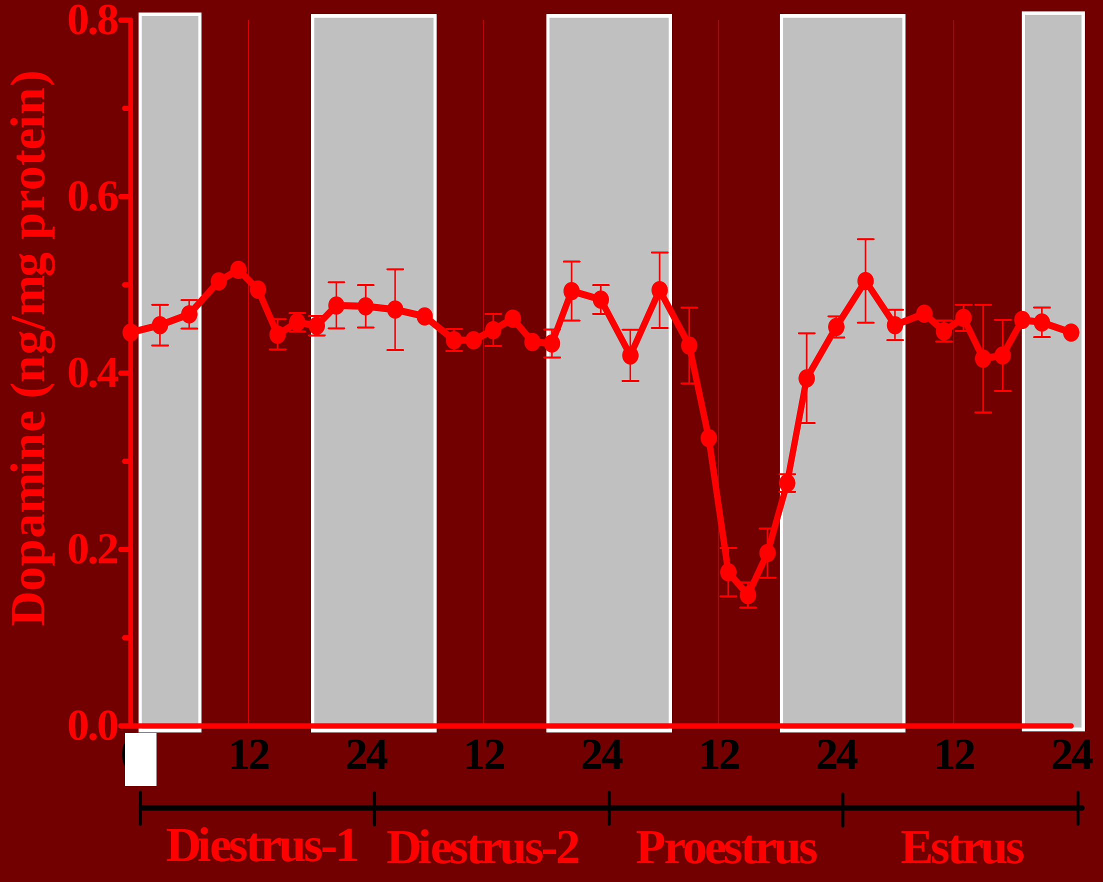
2. The prolactin rhythm can be induced by mating, or in OVX animals, by cervical stimulation, central or peripheral prolactin injection, or peripheral oxytocin injection.

3. Oxytocin at the lactotroph is necessary for the expression of the CS-induced rhythm, but is not part of the triggering mechanism.

Prolactin Secretion During Rat Estrous Cycle



The Amount of Dopamine Arriving in the Anterior Lobe Decreases Coincident with the Rise of Prolactin During the Estrous Cycle



Does Oxytocin Contribute to the Proestrous Surge?

1. Plasma oxytocin concentration increases in response to estradiol administration (Yamaguchi et al., Endocrinol. Jpn., 26:197, 1979)

2. The concentration of oxytocin in pituitary portal blood peaks on the afternoon of proestrus (Sarkar and Gibbs, Neuroendocrinology, 48:214, 1988)

So a role for oxytocin seems plausible

Does the Oxytocin Sensitivity of Lactotrophs Vary During the Cycle?

Our experiments:

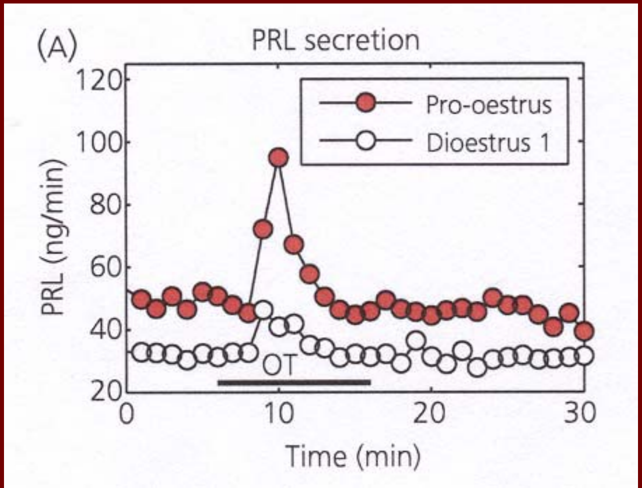
Remove anterior pituitaries from cycling rats on the morning of diestrus-1 or afternoon of proestrus

Disperse cells. Use mixed population for prolactin secretion measurements, enrich for lactotrophs for calcium measurements

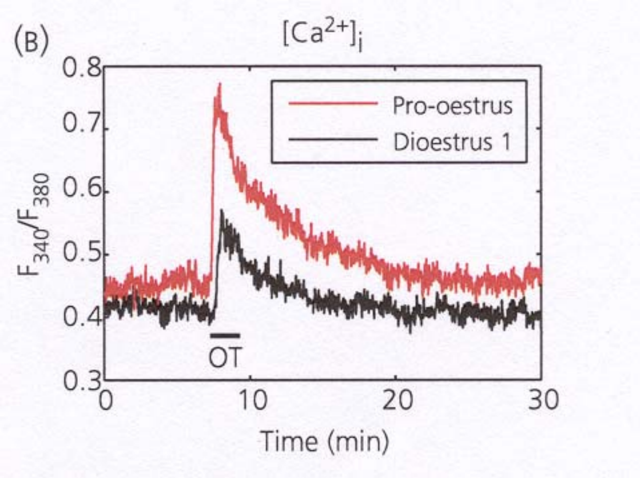
Apply oxytocin to the pituitary cells

Response to Oxytocin is Greater from Proestrous Cells

Secretion increased



Calcium response increased



Tabak et al., Endocrinology, 151:1806, 2010

Conclusions: Part 2

1. Sensitivity of lactotrophs to oxytocin is increased during the afternoon of proestrus. This corresponds to the time of the peak in plasma oxytocin levels, and the prolactin surge.

2. Both the size of the individual calcium responses and the number of cells responding to oxytocin are upregulated on the afternoon of proestrus.

Open Question: What is the mechanism of the upregulation of the oxytocin response?

A review of this talk is freely available online in the July Special Issue:

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