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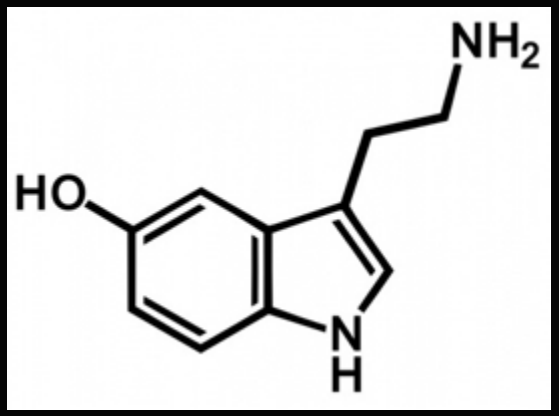

A Novel Method to Prevent Hypocalcemia? Can we improve cow longevity and health in the herd?

Laura L. Hernandez, Ph.D.

Culling During Early Lactation

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- 75% of production diseases occur in the 1st month after calving (LeBlanc et al., 2006)
- 25% of all herd losses occur during the first 60 DIM (Nordlund and Cook, 2004; Godden et al., 2012)
- The majority leave due to involuntary reasons such as (Grummer et al., 2004; Nordlund, 2006; Mulligan and Doherty, 2008):
  - Death (35%)
  - Injury/disease (30%)

When Cows Leave the Herd and Risk of Leaving the Herd

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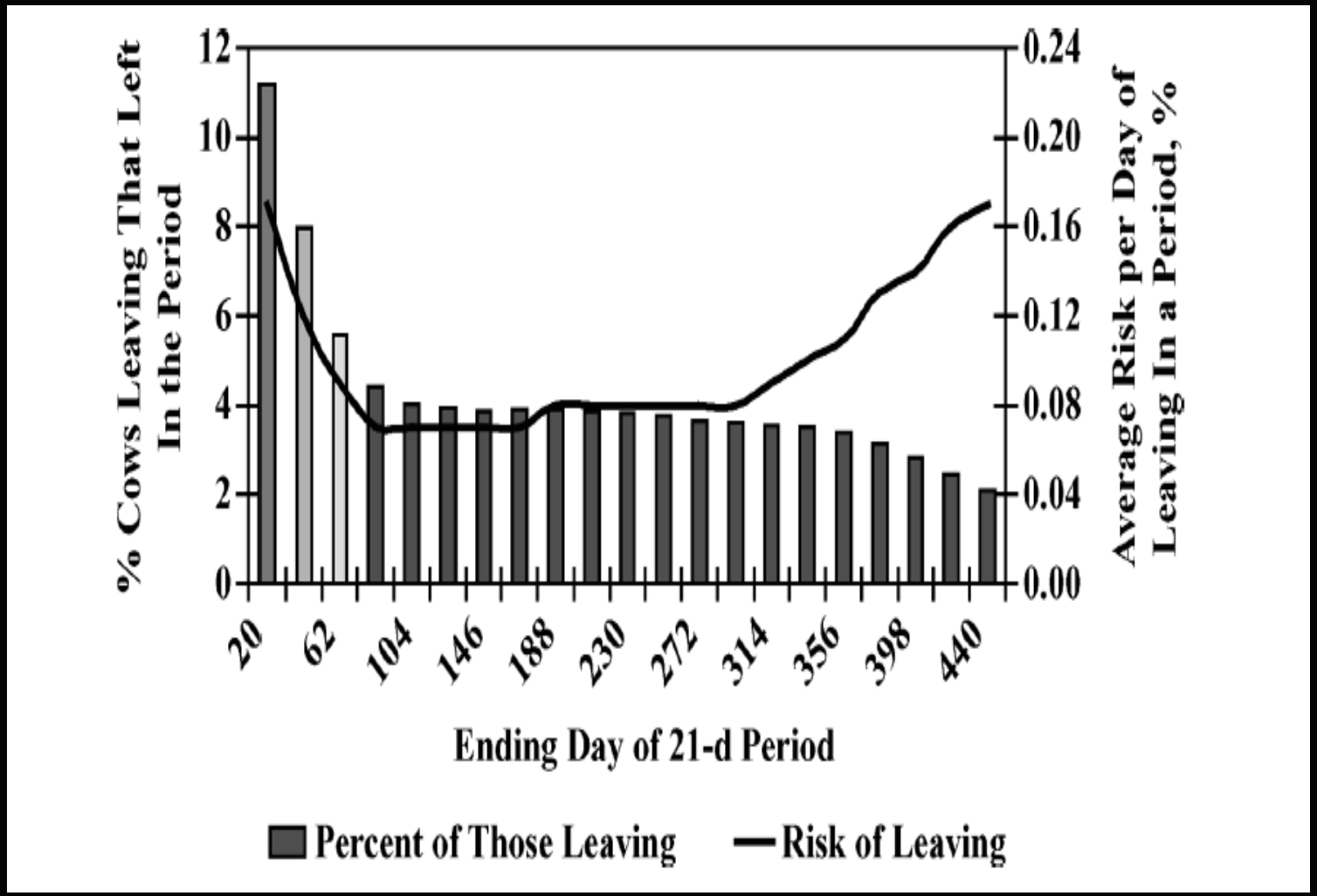

Godden et la., 2003; Fetrow et al., 2006

Disease Incidence in Dairy Cows During the first 60 DIM

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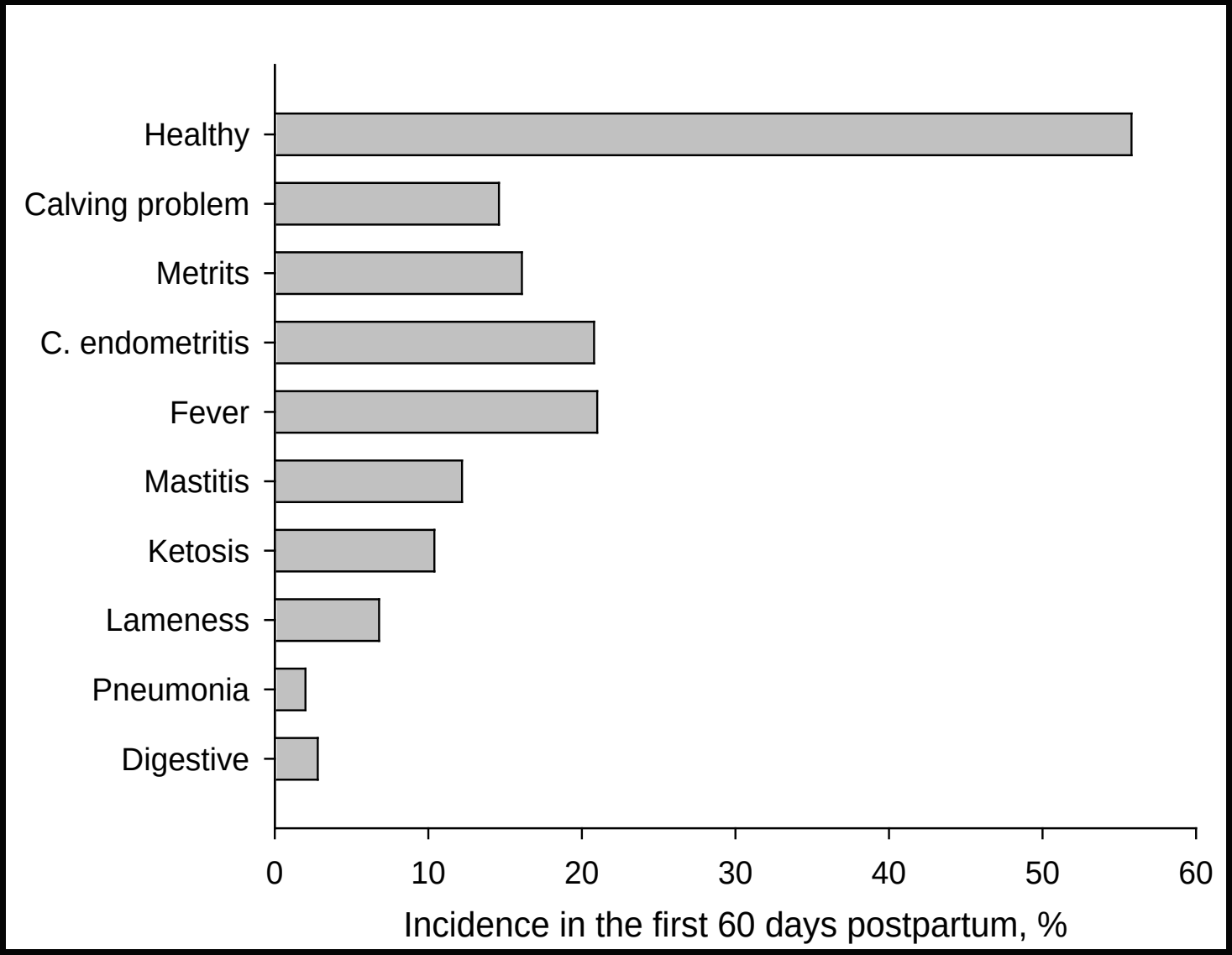

McConnell et al., 2009

Importance of Calcium in Lactation

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- Milk provides calcium needed for rapid skeletal growth in offspring
- 80g/day into milk during lactation (~2x more in colostrum)
- Calcium partially comes from increased absorption of intestine of calcium
- Some is provided by kidney retention of calcium
- Primary contributor is release of calcium **from bone** (negative feedback)
  - 9-13% of bone mass lost in cattle (Goff, 2008)
  - Reversible bone loss (lactational specific osteoporosis)
  - This is thought to be primarily controlled by parathyroid hormone related-protein (PTHrP) production in the mammary gland, may be involvement of PTH/Vitamin D as well

Change in Calcium Status at Parturition

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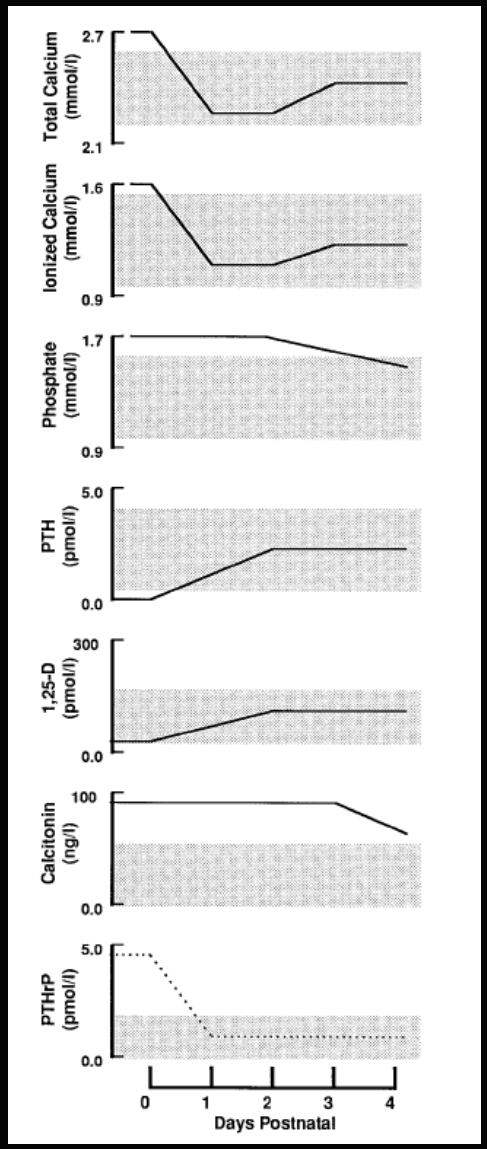
- During **late pregnancy** calcium is lost from the blood to the fetus at a rate of 80 mg/kg$^{3/4}$ (Horst et al., 2006)
- During **early lactation** calcium is lost from the blood to the milk at a rate of 500 mg/kg$^{3/4}$ (Horst et al., 2006)
- Cows will deplete their blood pool of calcium 20-30x per day in order to put sufficient calcium into milk (Goff, 2008)
- Right at calving, bone resorption is decreased in dairy cattle (Horst et al., 2006)
- Lose calcium much more quickly than other species due to complete milk removal at 2-3x/day



Kovacs and Kronenberg, 1997

Calcium Flux During Lactation

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Active Transport

Extracellular Ca Pool: 11 g

7.8-8.5 kg

<u>Dietary Ca</u>:
45-150 g

3-3.5 g
Ca^{2+}

Passive Transport

20-30g

9-13% Bone Mass lost during 1st 30 DIM

<u>Colostrum Ca^{2+}</u>: 1.7 g-2.3g/kg
<u>Milk Ca^{2+}</u>: 1.1 g/kg

Hypocalcemia

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Smooth muscle function

Immune function

Rumen and GIT motility

Uterine motility

Teat sphincter contraction

Feed intake

Dystocia (RFM)

Mastitis

Milk yield

Metritis

Energy balance

Rumen fill

Uterine involution

Displaced abomasum

Ketosis
Fatty liver

Reproduction

- **Reduced pregnancy rates**
- **Longer intervals to pregnancy** (Martinez et al., 2012)
- **Production losses ~14%** (Guard, 1996)

Goff, 2008; Martín-Tereso and Verstegen, 2011; Chapinal et al., 2011

Hypocalcemia in dairy cattle

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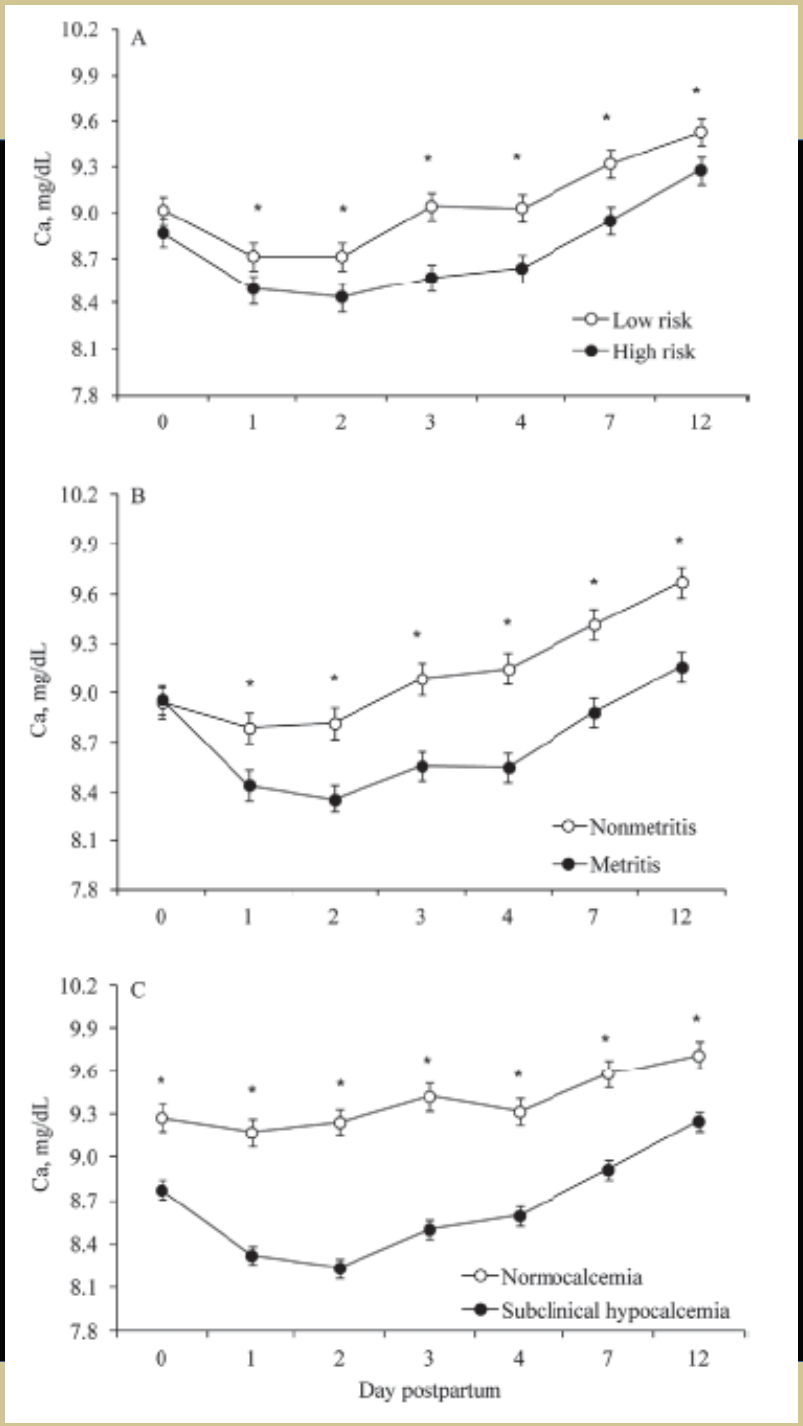
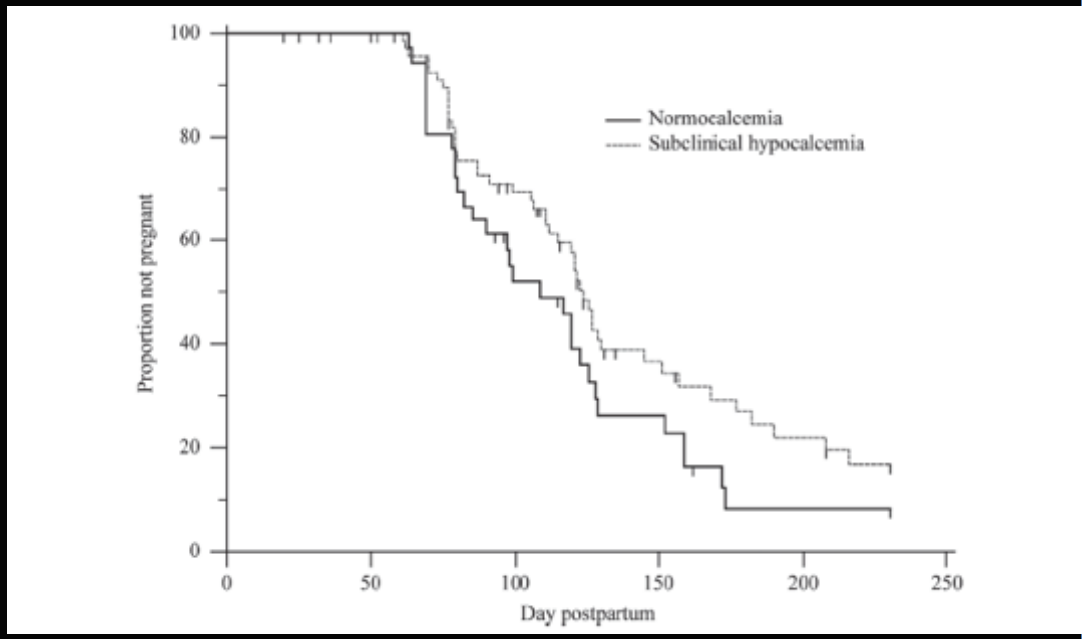
- US dairy industry suffers an estimated **loss** of **~$590m-730m per year** attributed to hypocalcemia (est. from Hare et al., 2006; Oetzel, 2013)

- Hypocalcemia has been associated with an **increased risk** of production losses, displaced abomasum, metritis, reproductive deficiencies, and ketosis (Adams et al., 1996)

- Recent study has shown <2.2mM total circulating blood Ca has been linked to increased risk of displaced abomasum (Chapinal et al., 2011)





Martinez et al., 2012

Table 1. Herd-level associations of increased metabolite concentrations in wk +1 relative to calving with displaced abomasum, controlling for region (n = 55 herds)

Metabolite	Herd-level threshold[1] (%)	Farms above threshold (%)	OR[2]	CI	*P*-value
All cows					
BHBA[3] ≥1,400 μmol/L	≥25	15	2.1	1.0–4.2	0.04
Calcium ≤2.1 mmol/L	≥35	24	2.4	1.3–4.3	0.003
Multiparous cows only					
BHBA[3] ≥1,400 μmol/L	≥25	21	1.8	1.0–3.3	0.04
Calcium ≤2.1 mmol/L	≥30	43	1.9	1.2–3.0	0.004

[1]Expressed as percentage of sampled cows in the high-risk metabolite concentration group.

[2]Odds ratio; odds of displaced abomasum in a high-risk herd (above the herd-level threshold) compared with a low-risk herd (below the herd-level threshold).

[3]Serum BHBA.

Table 2. Herd-level associations of increased metabolite concentrations in wk −1 and +1 relative to calving with milk production (kg/d) at the first DHIA test (n = 45 herds)

Metabolite	Herd-level threshold[1] (%)	Farms above threshold (%)	Estimate (kg/d per cow)	SE	*P*-value
All cows[2]					
wk −1					
BHBA[3] ≥800 μmol/L	≥15	16	−4.4	1.7	0.01
wk +1					
Calcium ≤2.1 mmol/L	≥15	73	−3.8	1.4	0.01
Multiparous cows only					
wk −1					
NEFA[4] ≥0.5 mEq/L	≥30	36	−3.0	1.5	0.04
BHBA[3] ≥800 μmol/L	≥20	11	−5.5	2.2	0.01
wk +1					
Calcium ≤2.1 mmol/L	≥25	55	−2.9	1.4	0.05

[1]Expressed as percentage of sampled cows in the high-risk metabolite concentration group.

[2]Controlling for the proportion of primiparous cows sampled in the herd.

[3]Serum BHBA.

[4]Serum NEFA.

Chapinal et al., 2012

How are the MG and bone systems inter-related? What are the systemic factors / signals?

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Calcium mobilization from bone is stimulated by mammary secretion of *parathyroid hormone-related protein* (PTHrP)

- Closely related at its N-terminal end to PTH
- Signals through the same GPCR
- Synthesized and secreted by "non-parathyroid gland tissues"
- Paracrine/autocrine factor
- Only detected in the circulation during lactation and during metastatic bone cancer

Ca movement in the mammary gland controls systemic Ca concentrations

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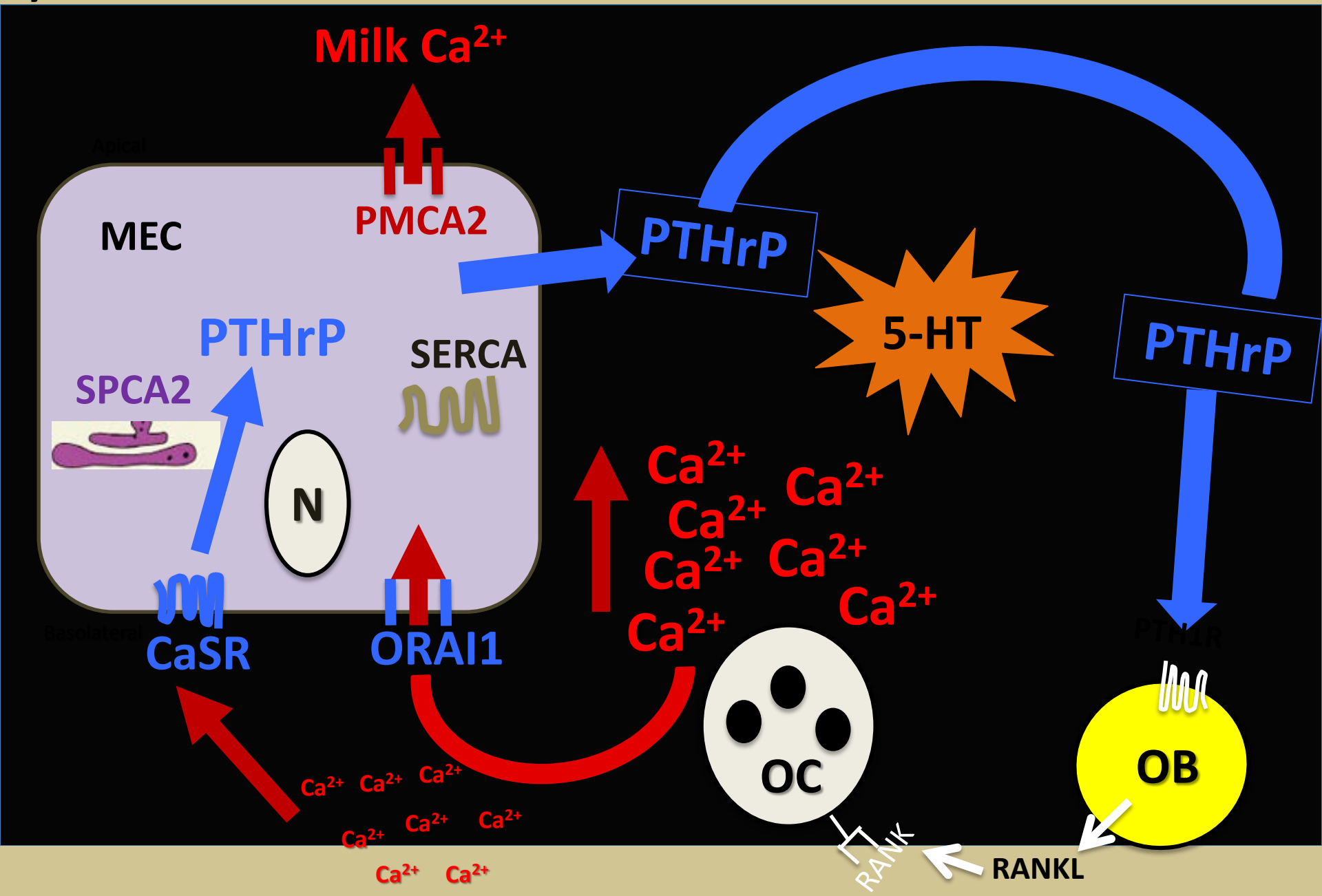

5-HT Synthesis

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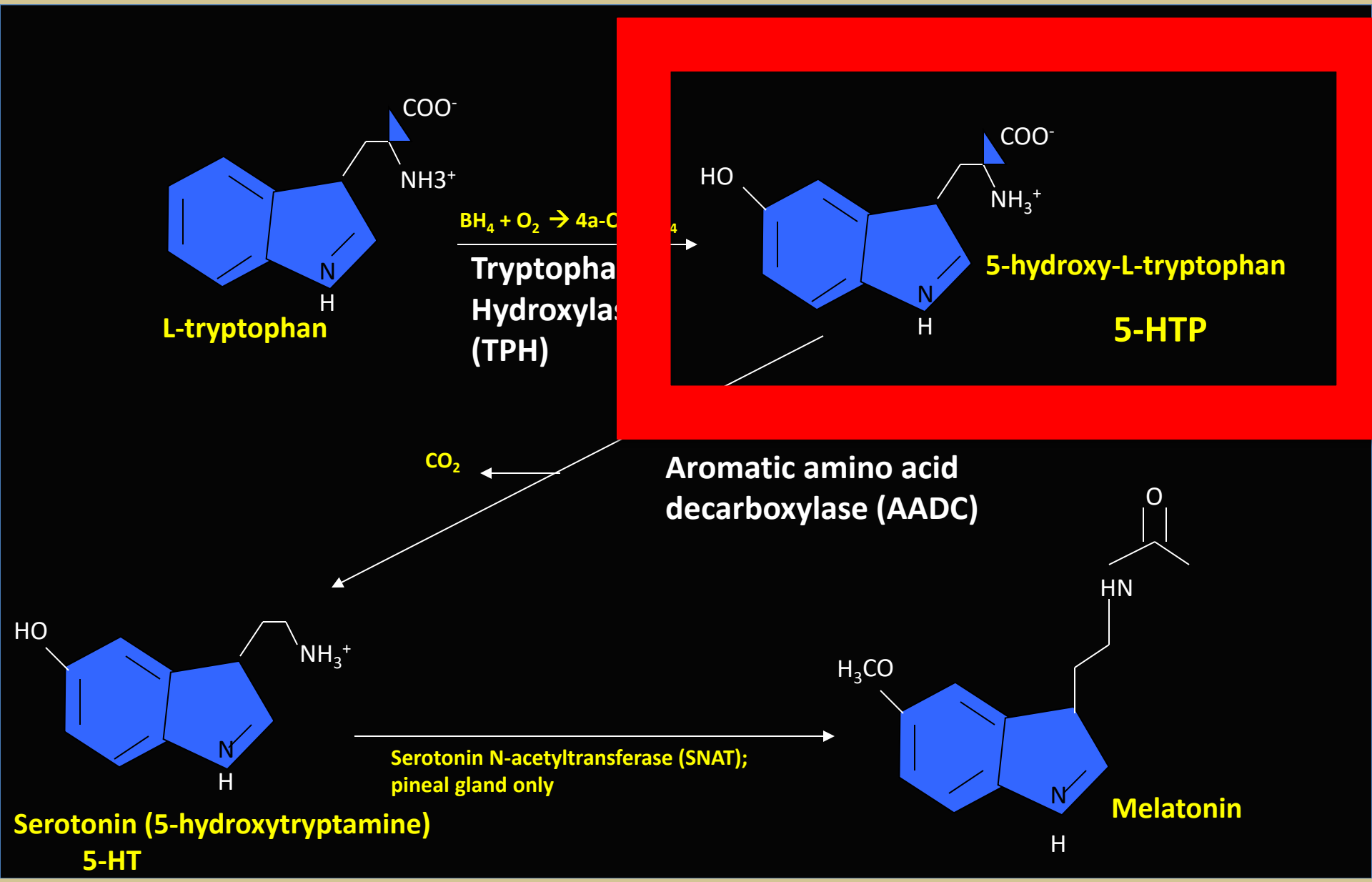

Adapted from Wang et al., 2002

How does mammary 5-HT contribute to bone turnover in lactation?

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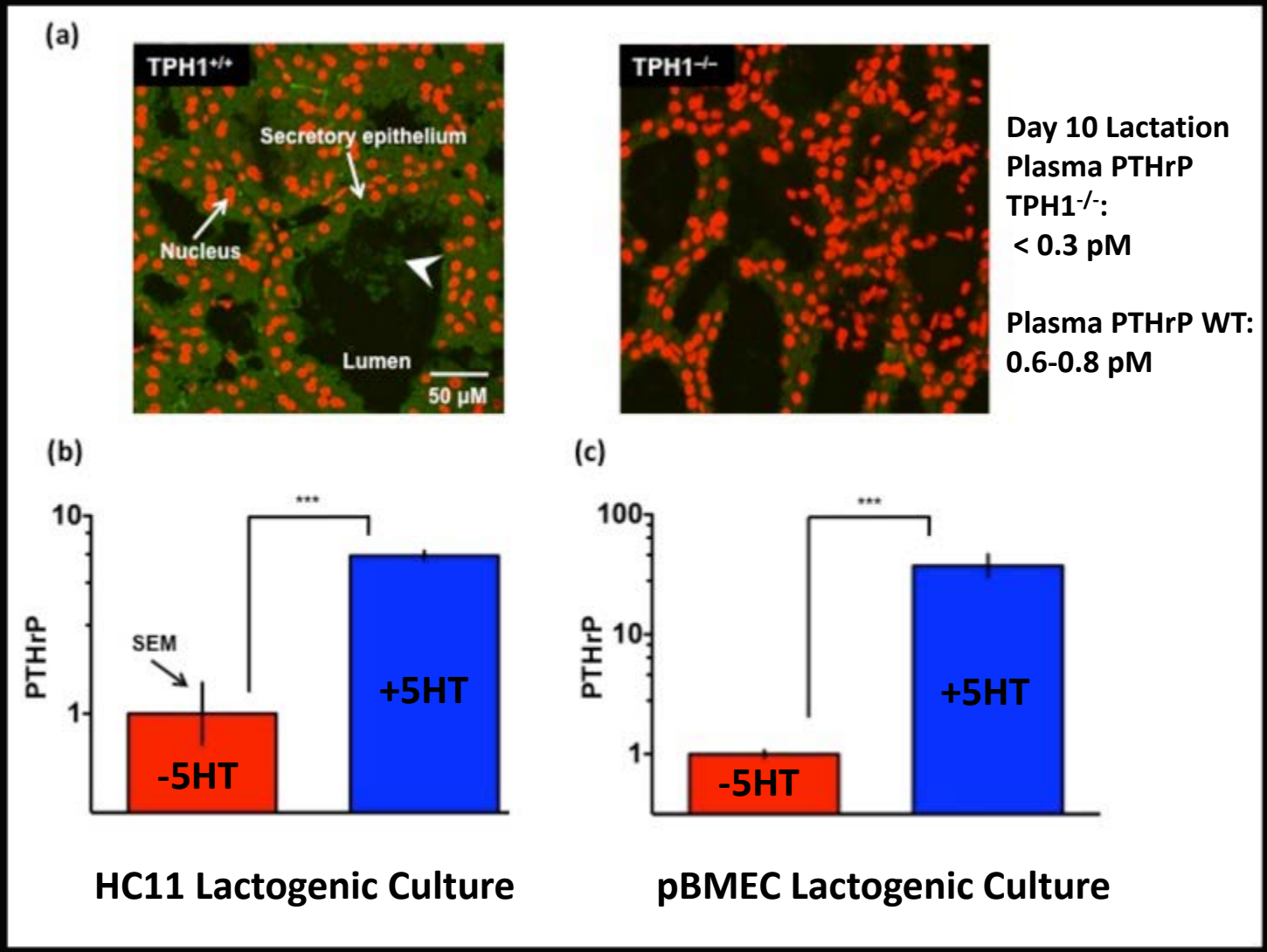

Hernandez et al. 2012, AJP

Relationship of 5-HT and Calcium on D1 Lactation in Dairy Cattle

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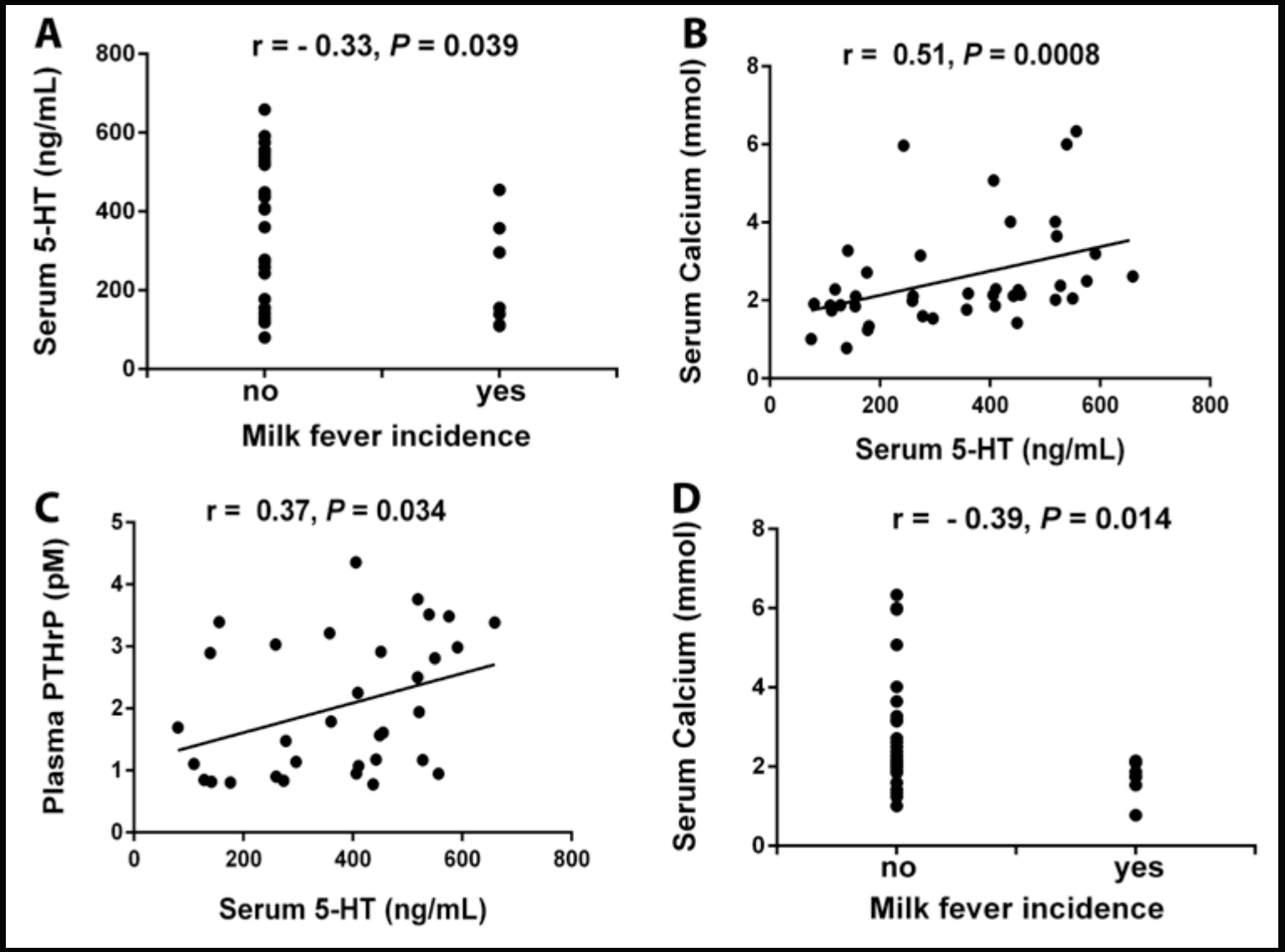

Laporta et al., 2013: Journal of Dairy Science

Farm 1-Jerseys

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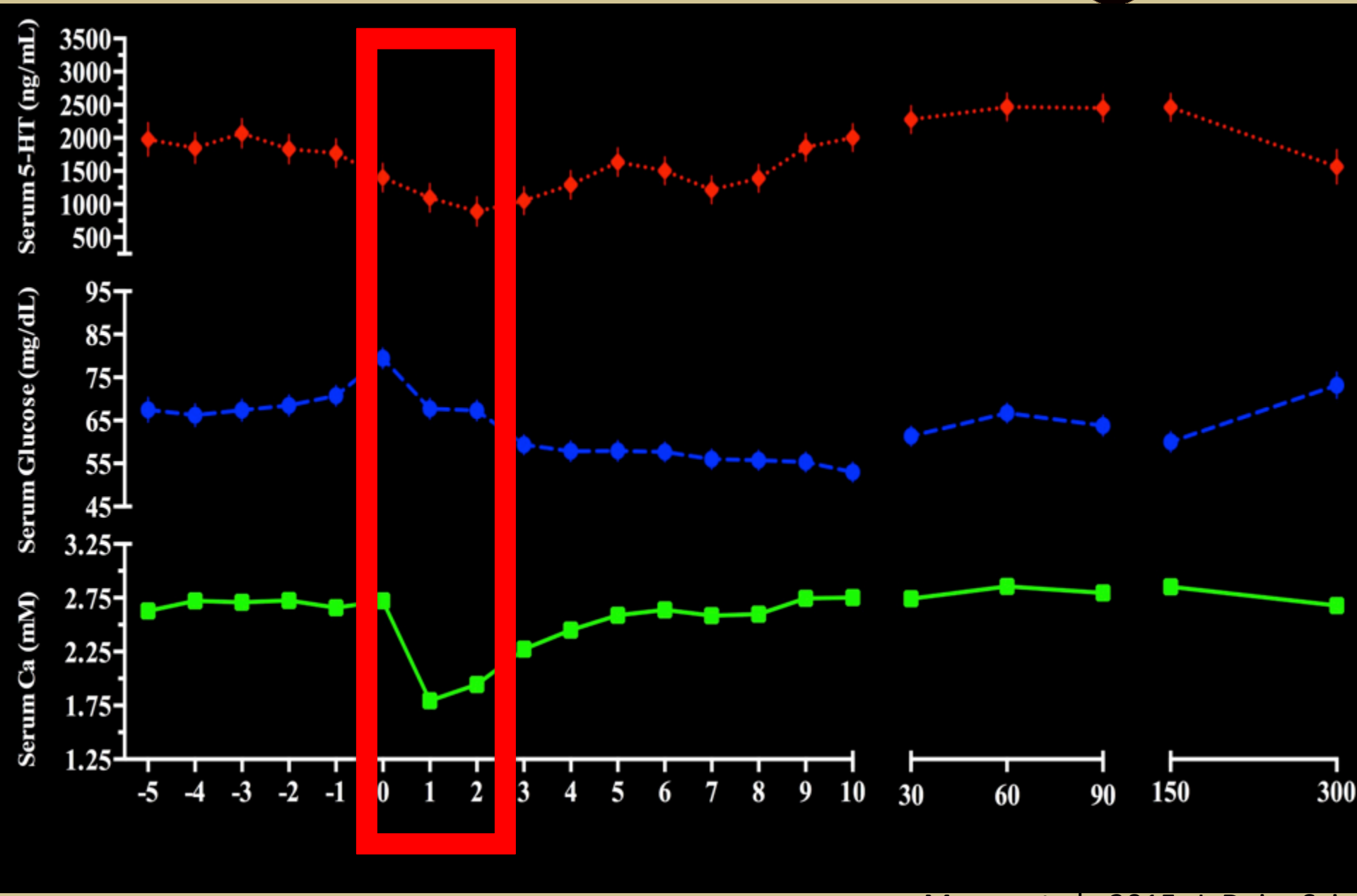
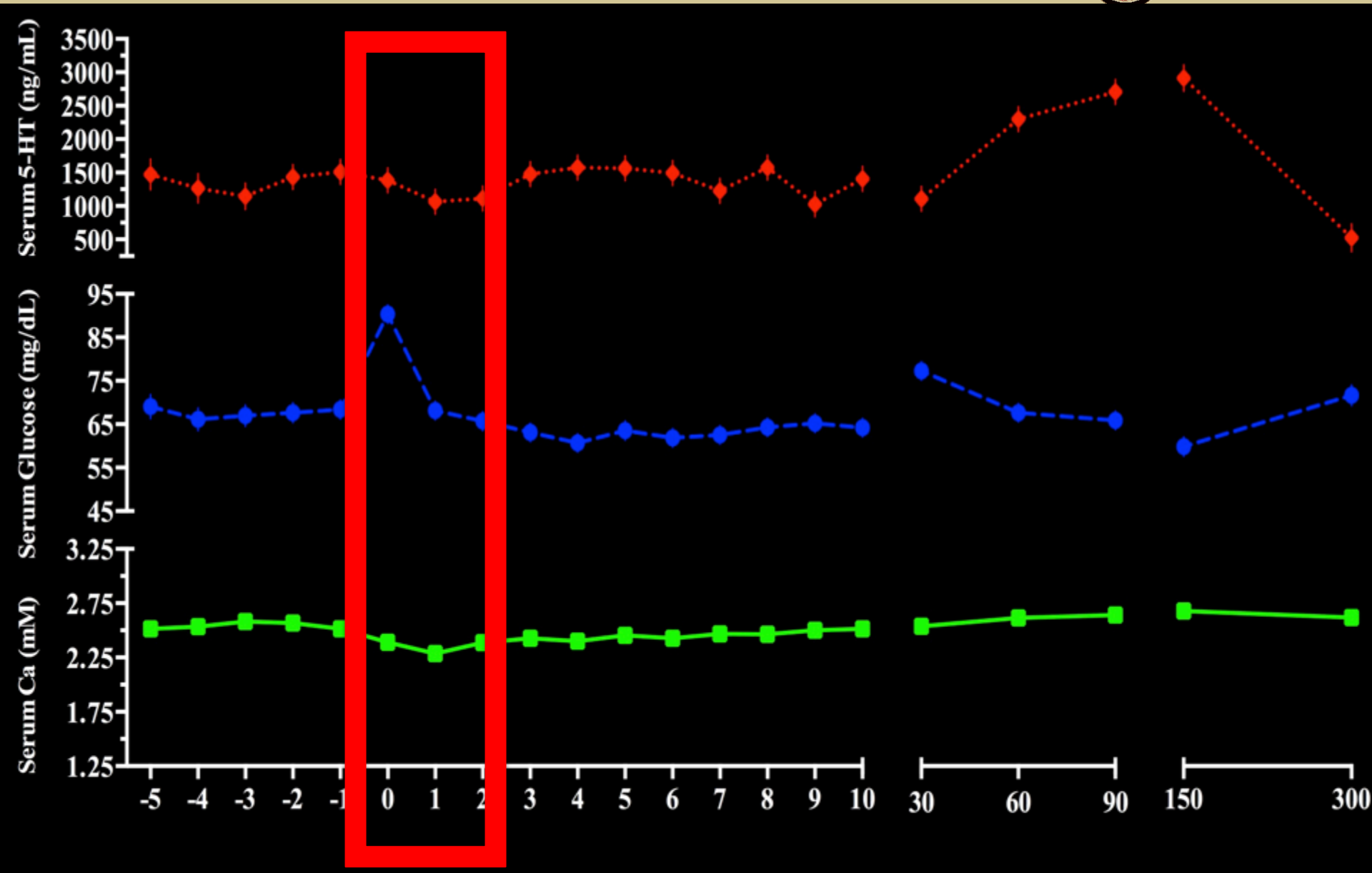


Moore et al., 2015; J. Dairy Sci

Farm 2-Holsteins



Moore et al., 2015; J. Dairy Sci

Can We Give Dairy Cows 5-HTP and Impact Calcium Metabolism?

Calcium Homeostasis in response to acute 5-HTP infusion

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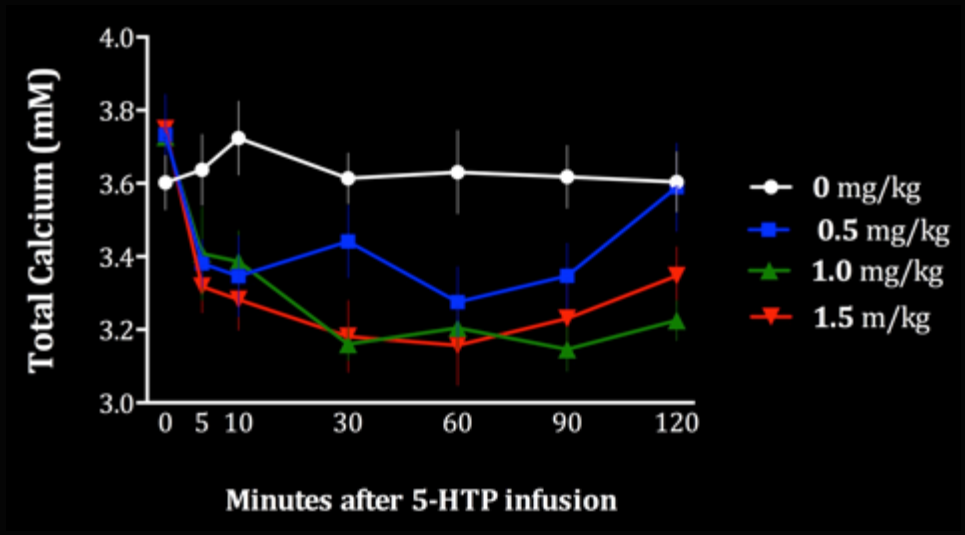
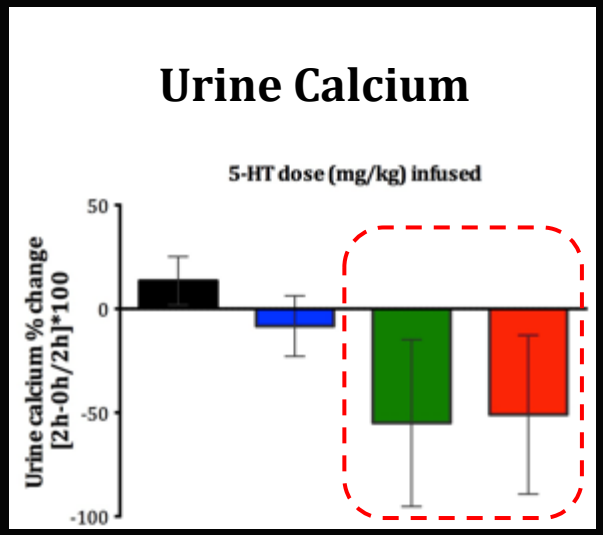
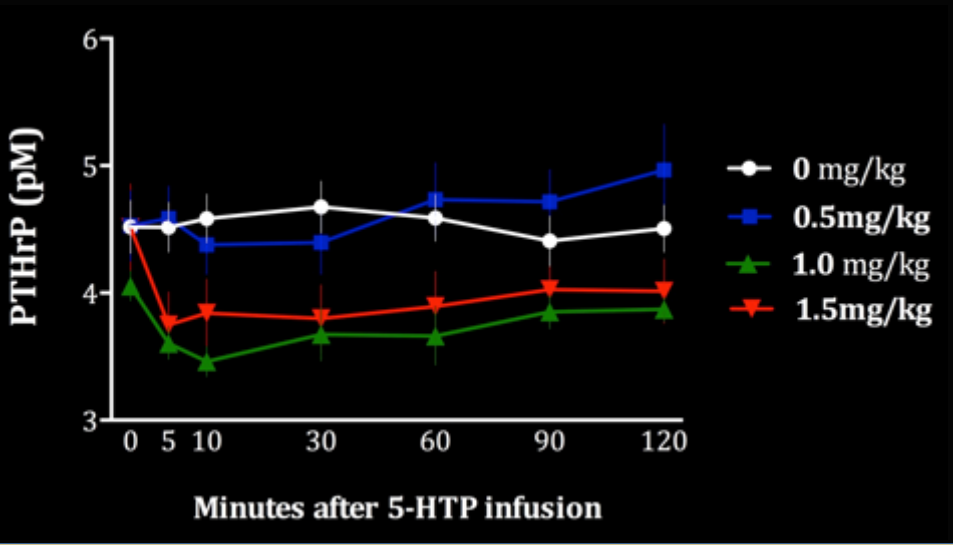
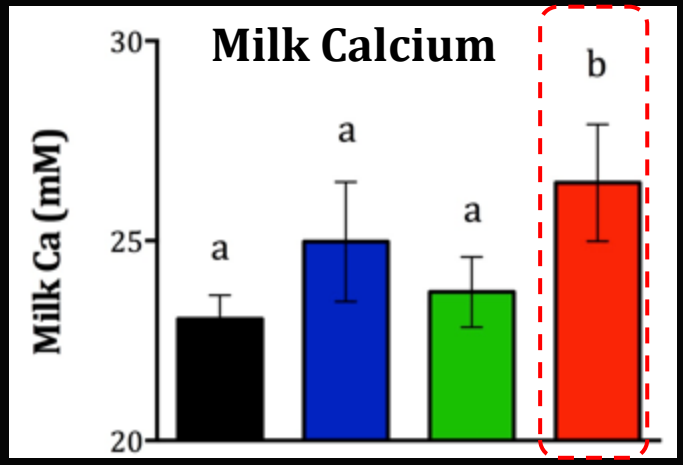
Calcium



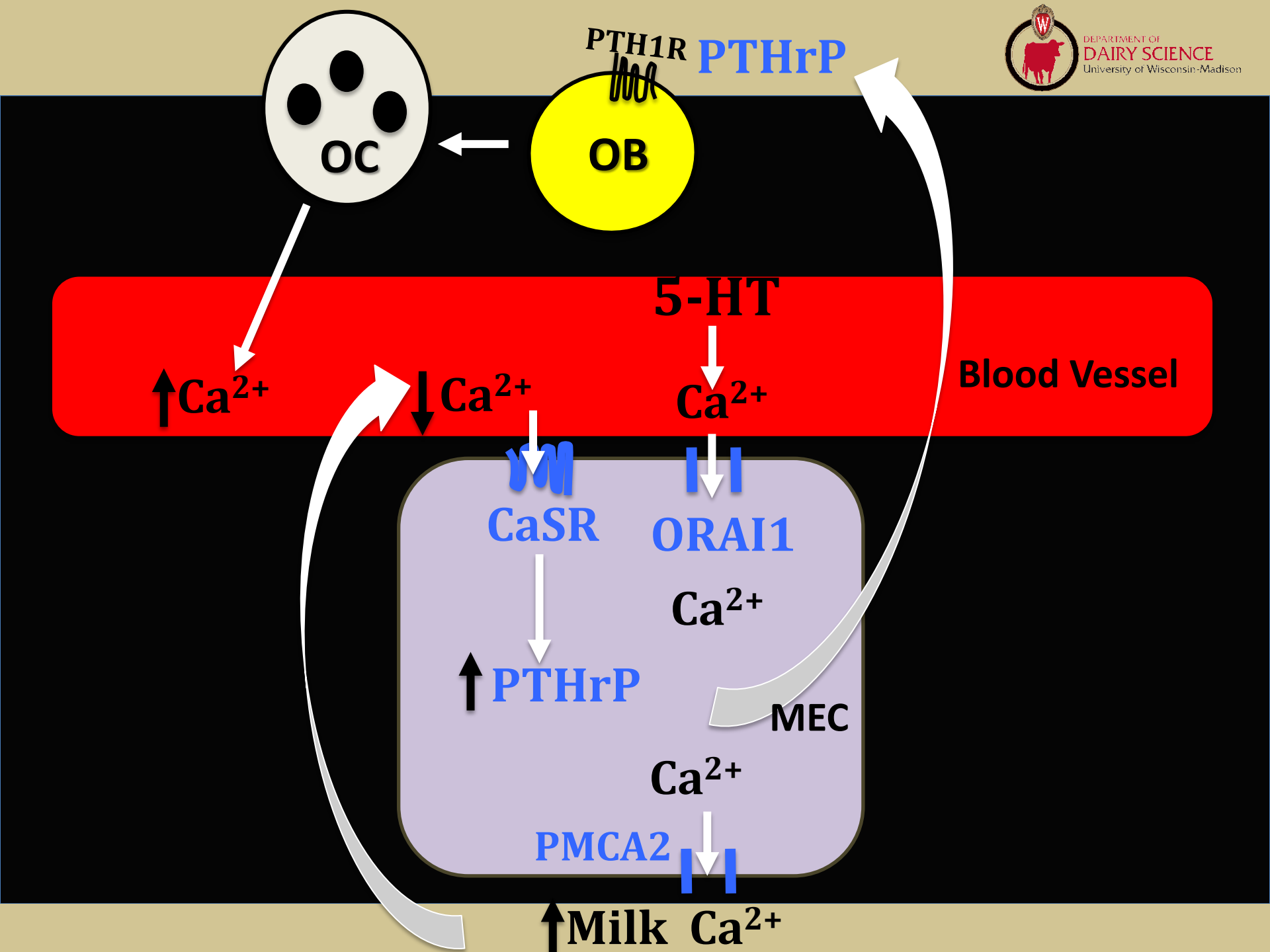


PTHrP





Laporta et al., 2015; J. Endocrinol.


PTH1R
PTHrP
OC
OB
5-HT
Blood Vessel
↑Ca2+
↓Ca2+
Ca2+
CaSR
ORAI1
Ca2+
↑PTHrP
MEC
Ca2+
PMCA2
↑Milk Ca2+

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Can We Give Dairy Cows 5-HTP and Impact Calcium Metabolism Post-Calving? Are there differences between how Holstein and Jersey Cows respond?

5-HTP infusion pre-calving improves Ca at Transition

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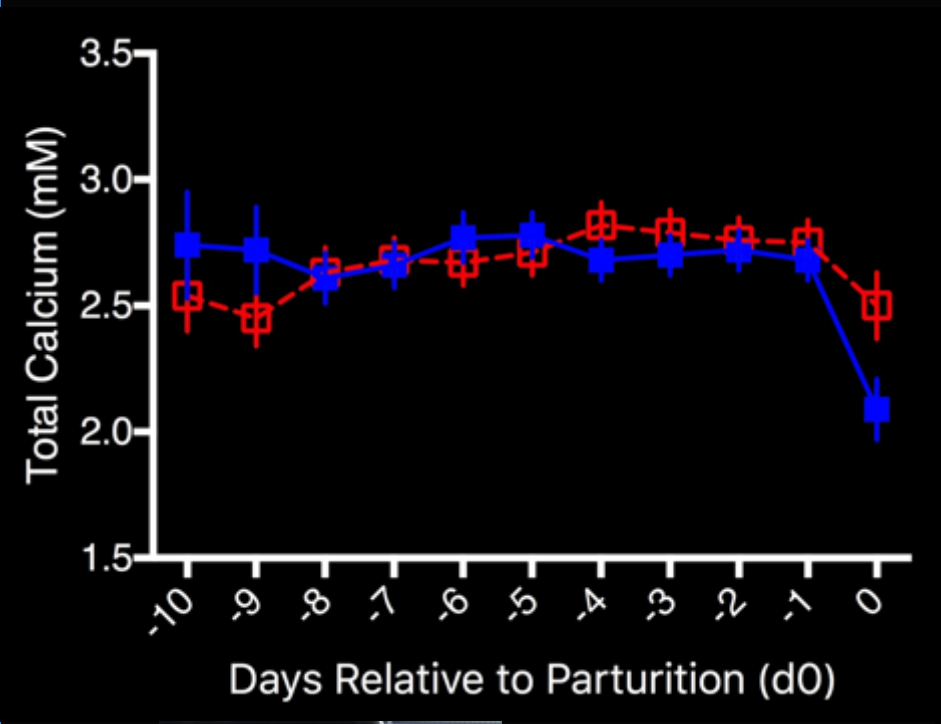

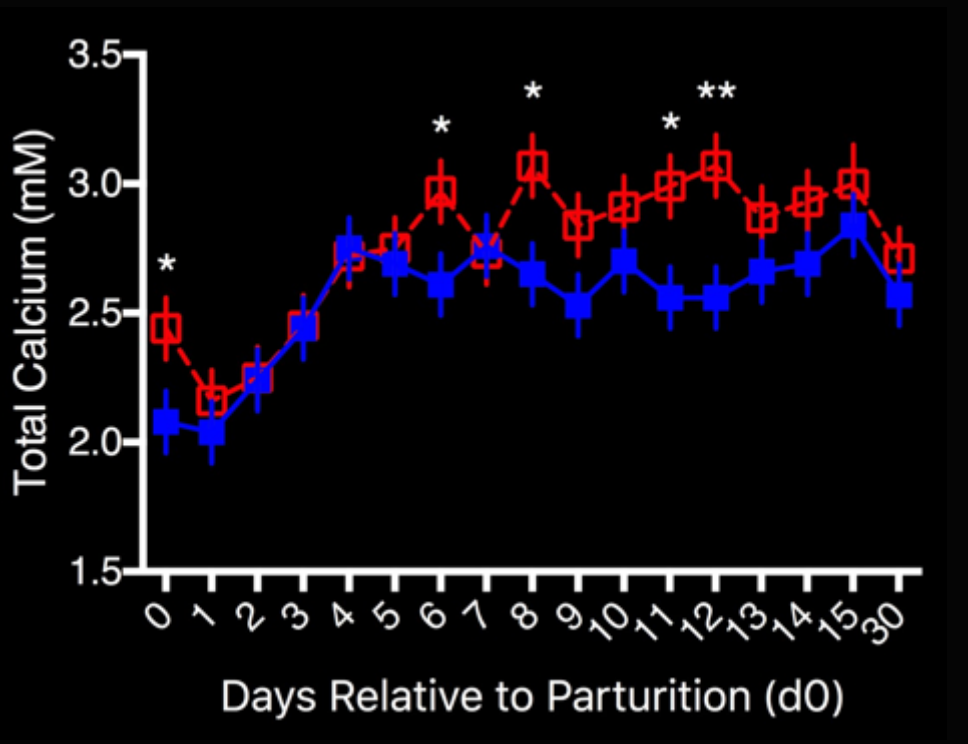

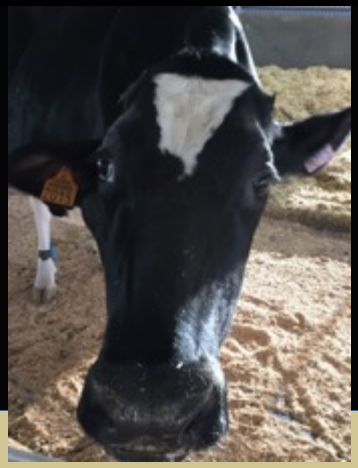

Weaver et al., 2016: J. Endocrinol.

5-HTP infusion pre-calving improves Ca at Transition

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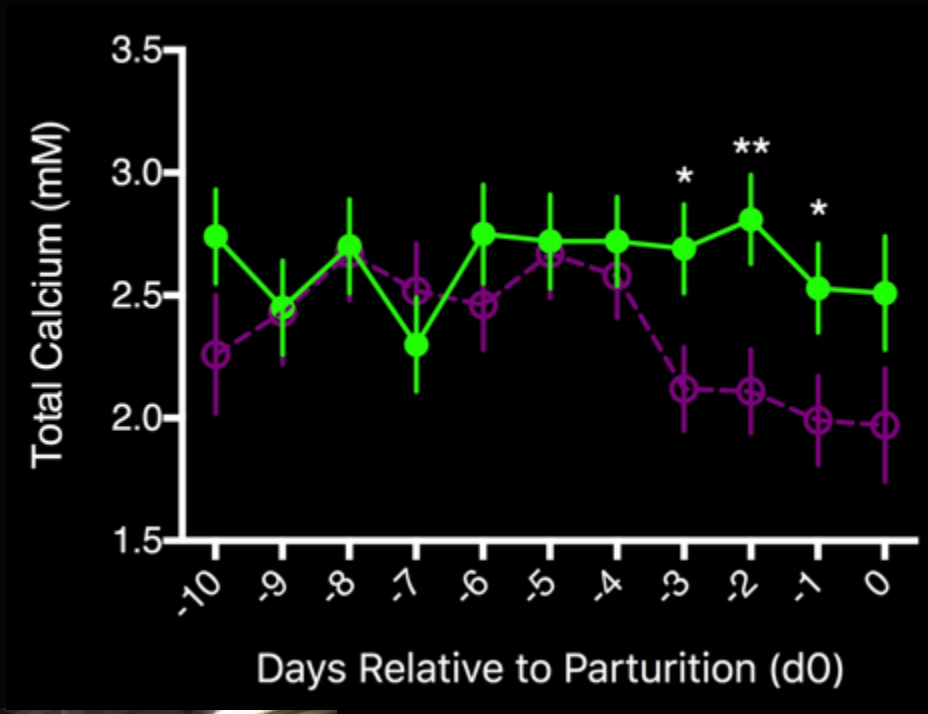

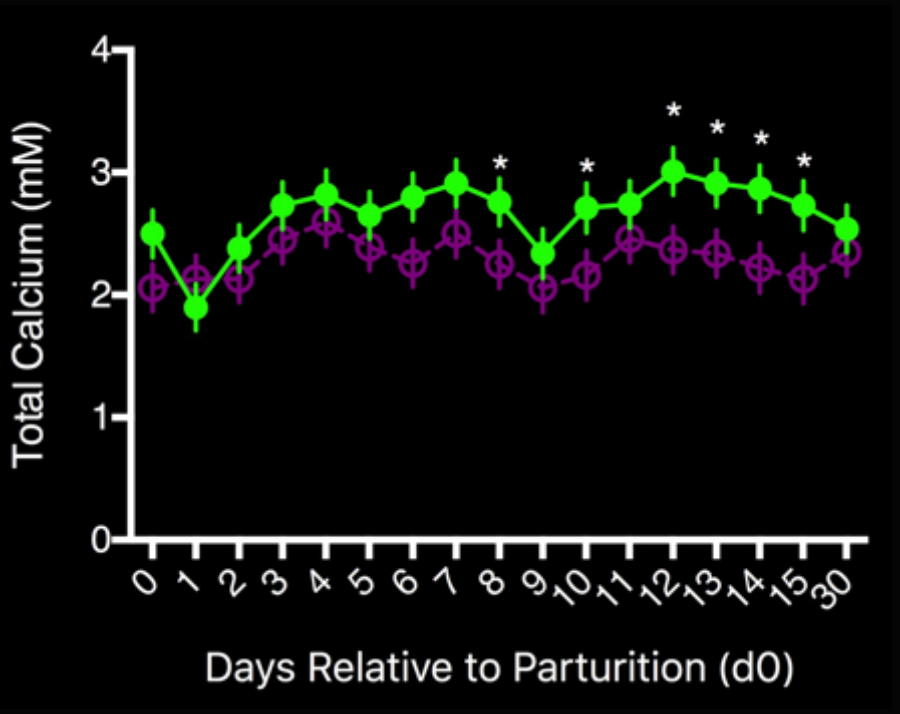

Weaver et al., 2016: J. Endocrinol.

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DAIRY SCIENCE AT WISCONSIN