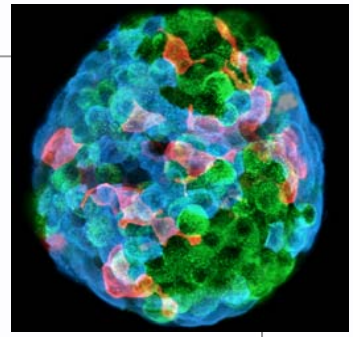


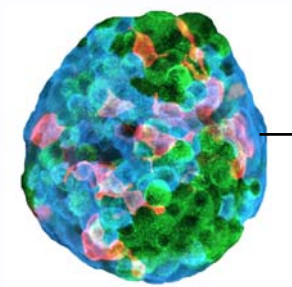
Adaptation of Islets to Pregnancy

Lessons from Islets as they adapt to pregnancy:

- Hormones and Lipids
- Insulin Secretion
  - Metabolism
    - Glucose
    - c-AMP
- Islet growth
  - mitosis
  - cell size
- Apoptosis
- Lipid plus Prolactin

Islet Adaptation to Pregnancy

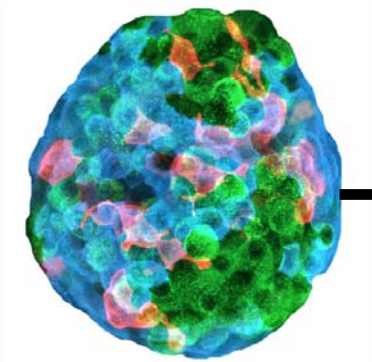
Control



Insulin

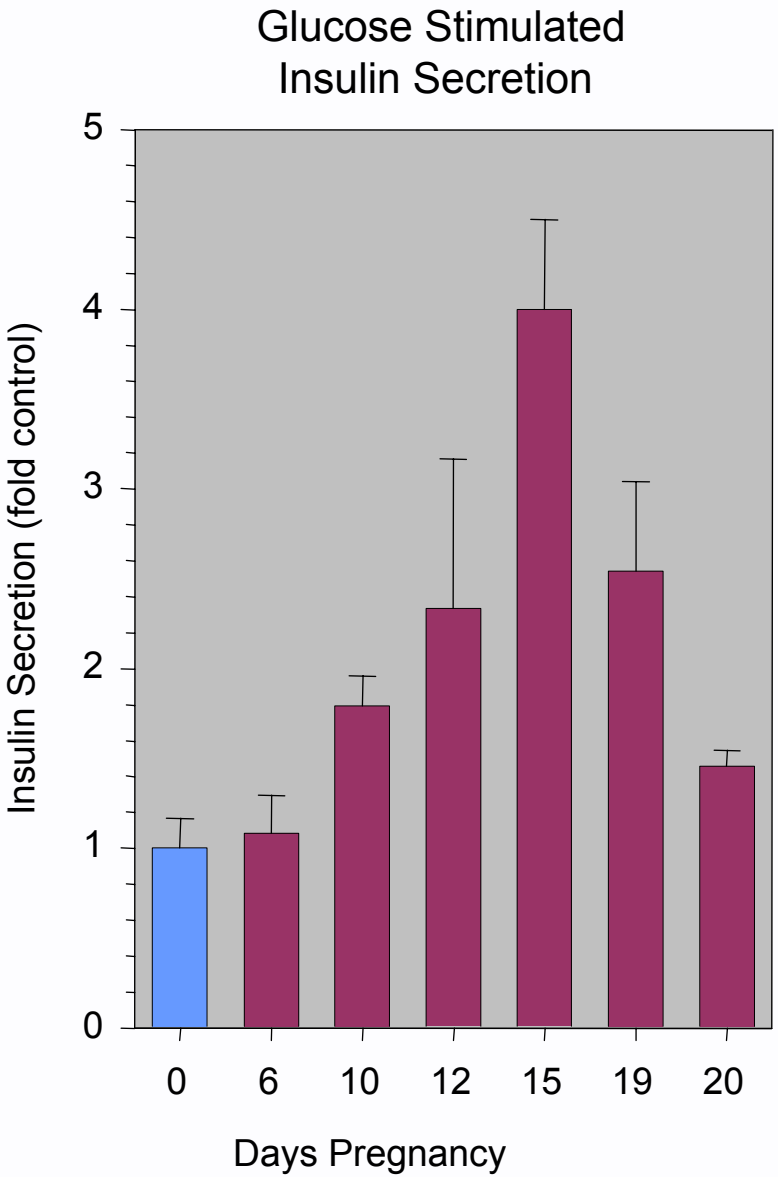
Fat
Muscle
Liver

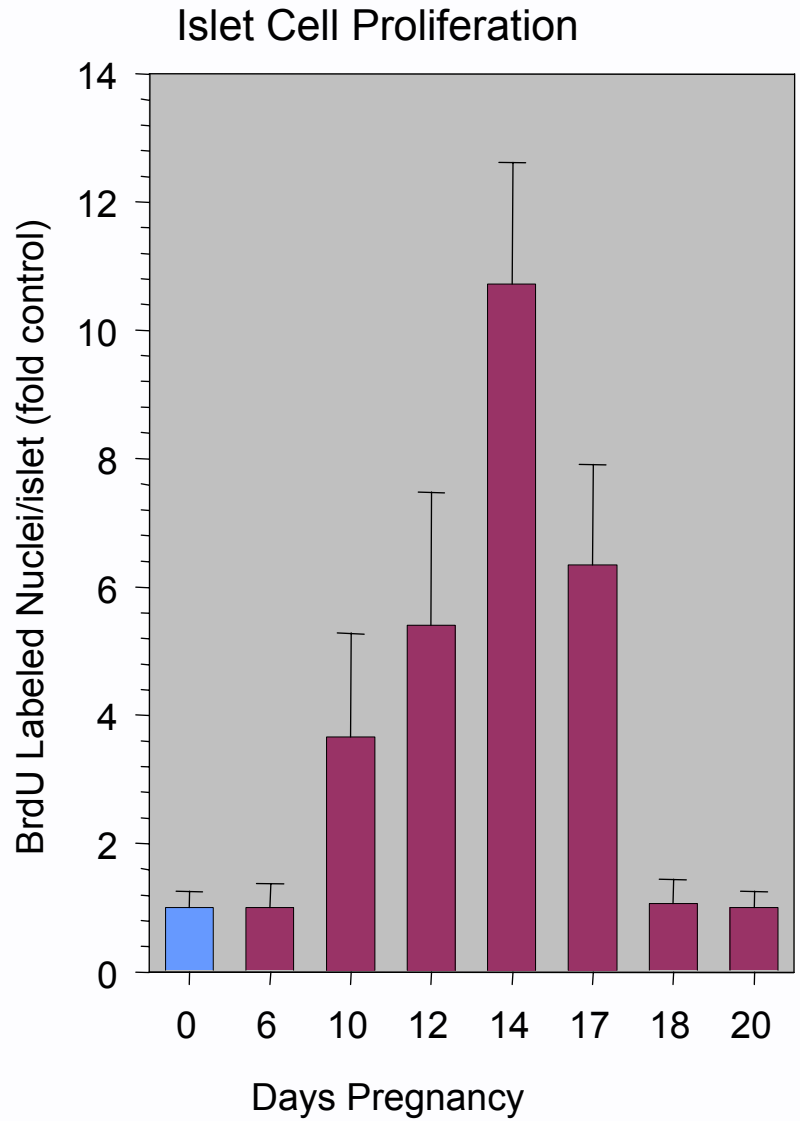
Pregnancy



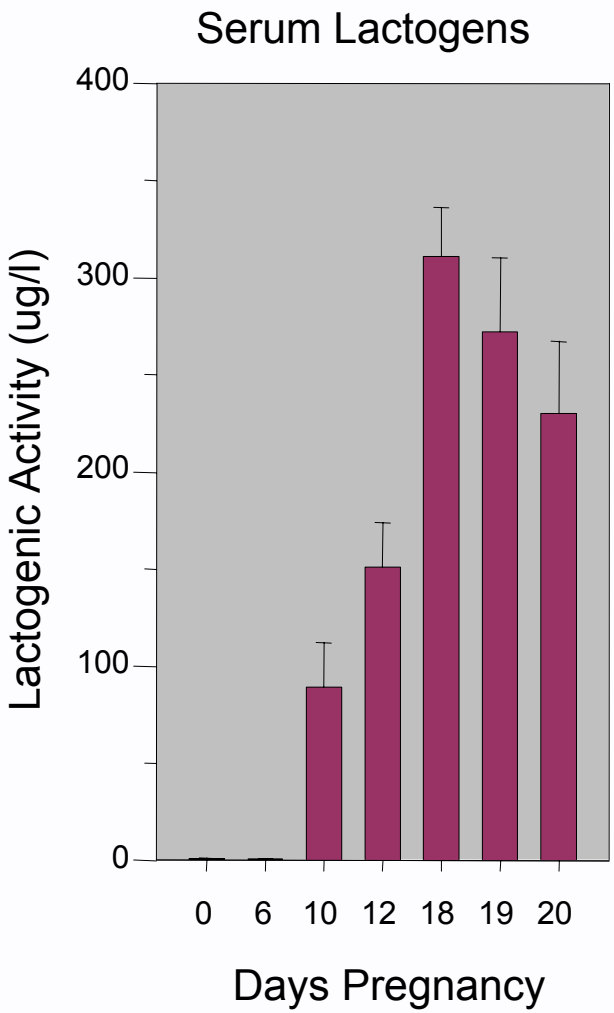
Fat
Muscle
Liver
Placenta

Glucose-Stimulated Insulin Secretion and Islet Cell Proliferation During Pregnancy





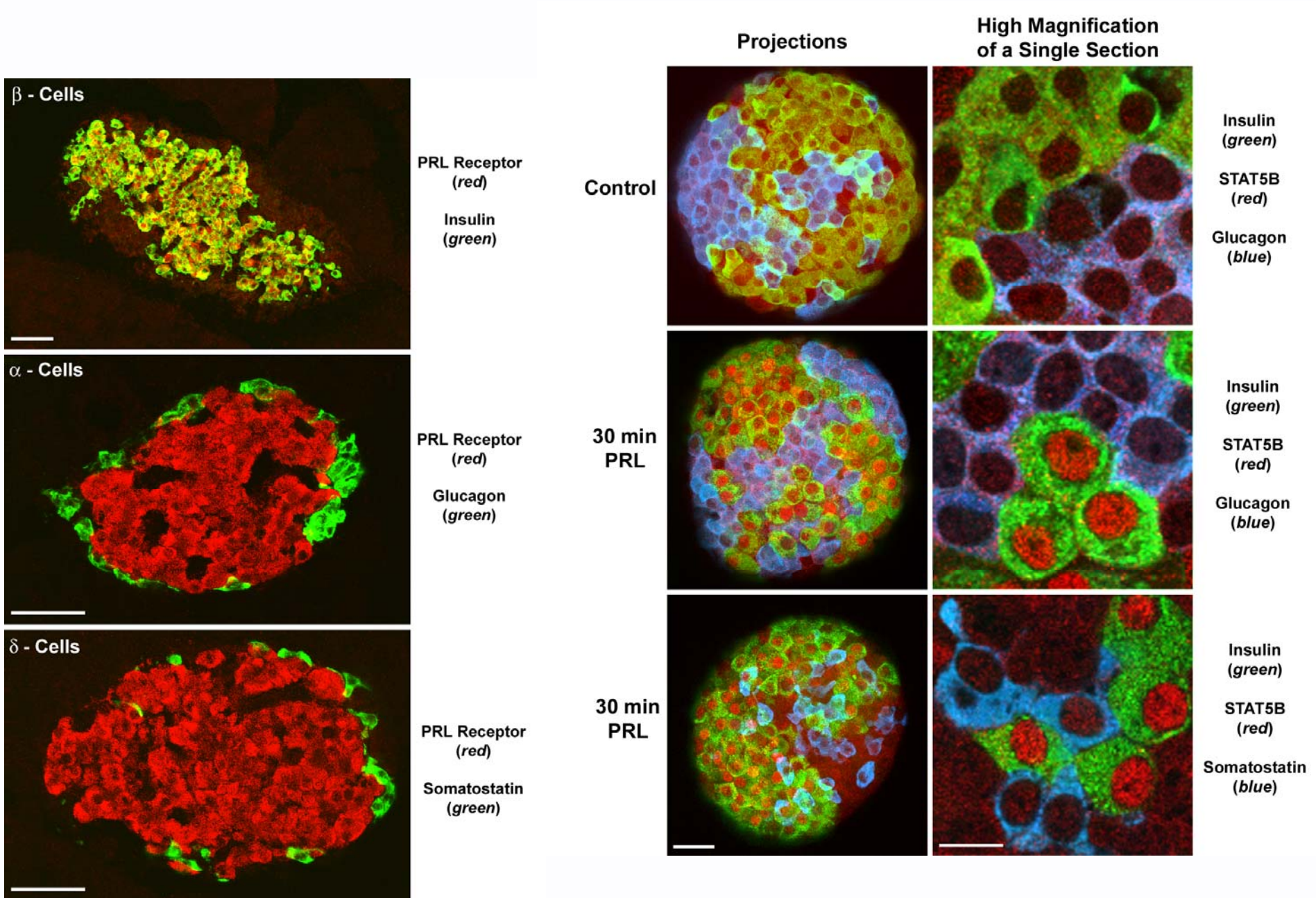
Placental Lactogen Levels during Pregnancy and its Effects on Islets



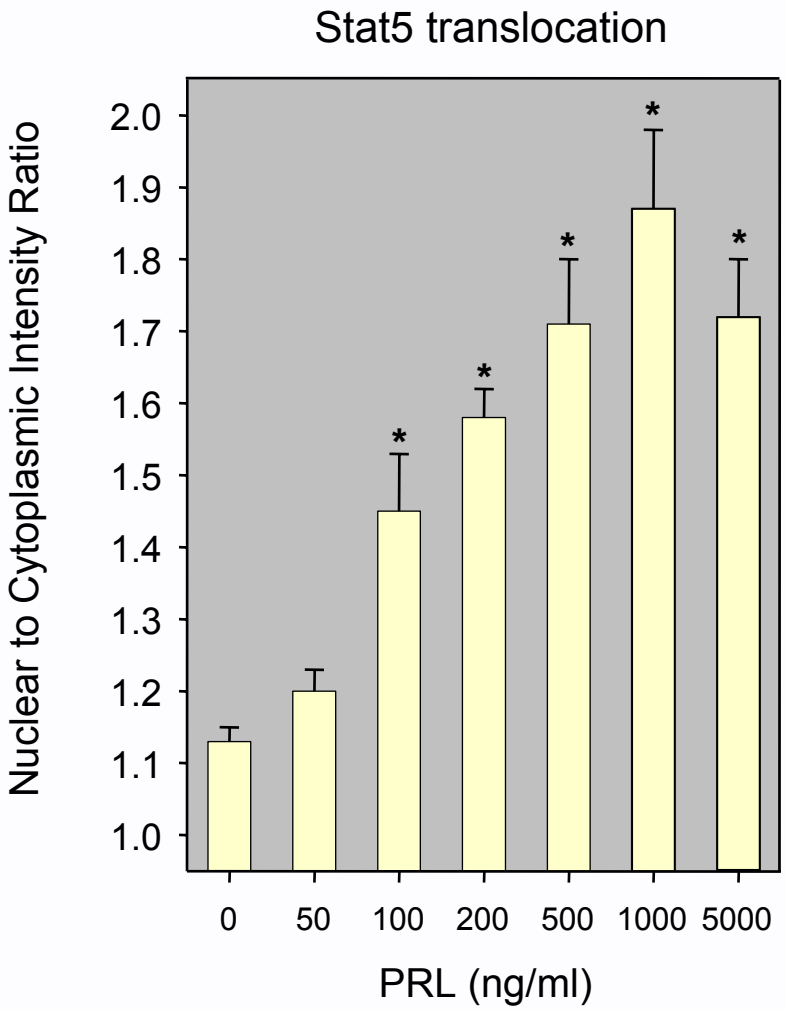
Effects of Pregnancy and Lactogenic Hormones on Islets

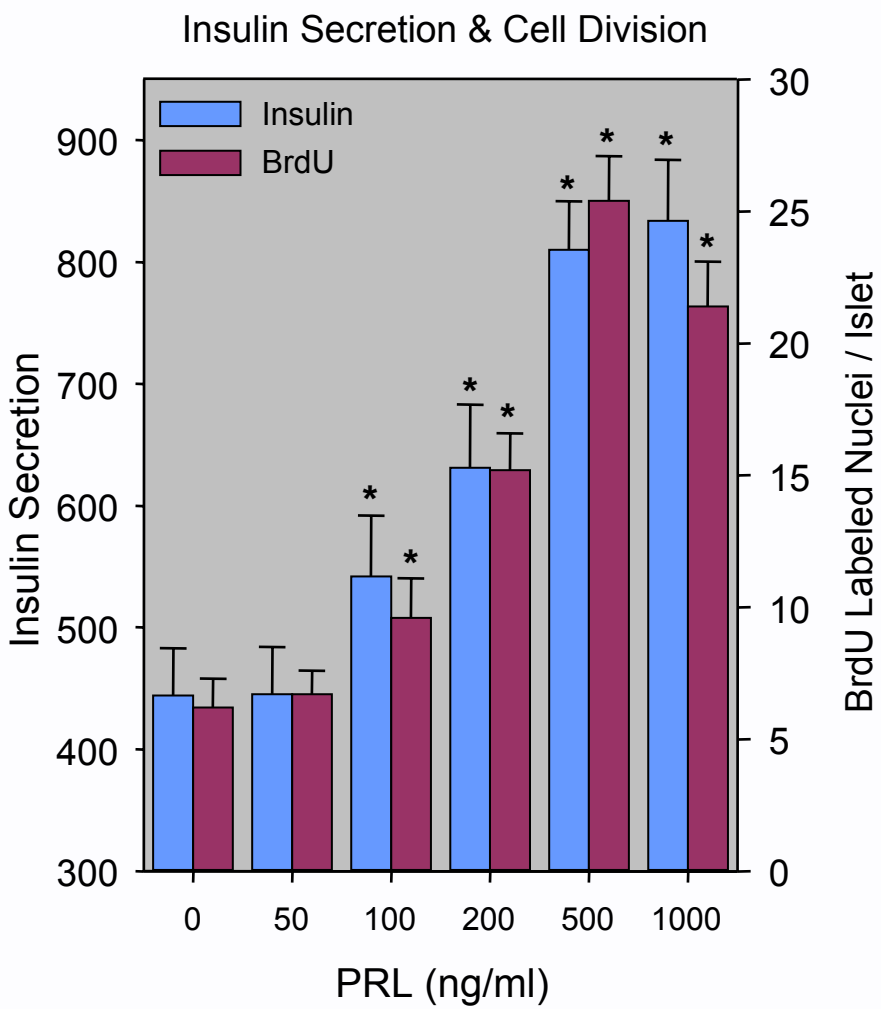
Islet structure and function	*Pregnancy*	*PRL/PL*	*Serum Lipids*
β-cell proliferation	+++	+++	
Islet volume	+++	+++	
Glucose stimulated insulin secretion	+++	+++	
Lower threshold for insulin secretion	+++	+++	
Insulin synthesis	+++	+++	
Insulin content	+++	+++	
β-cell junctional coupling	+++	+++	
Glucose utilization	+++	+++	
Glucose oxidation	+++	+++	
Glucokinase activity	+++	+++	
Glucose transporter 2	+++	+++	
c-AMP metabolism	+++	+++	
Anti-apoptosis	?	+++	

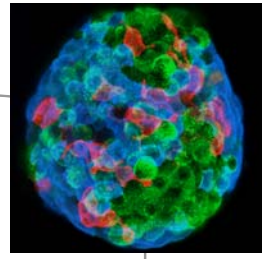
Prolactin Receptors in Islets and Prolactin Stimulated Stat5 Translocation in β-cells



Dose/Response for Prolactin Induced STAT5b Translocation and Changes in Islet Function



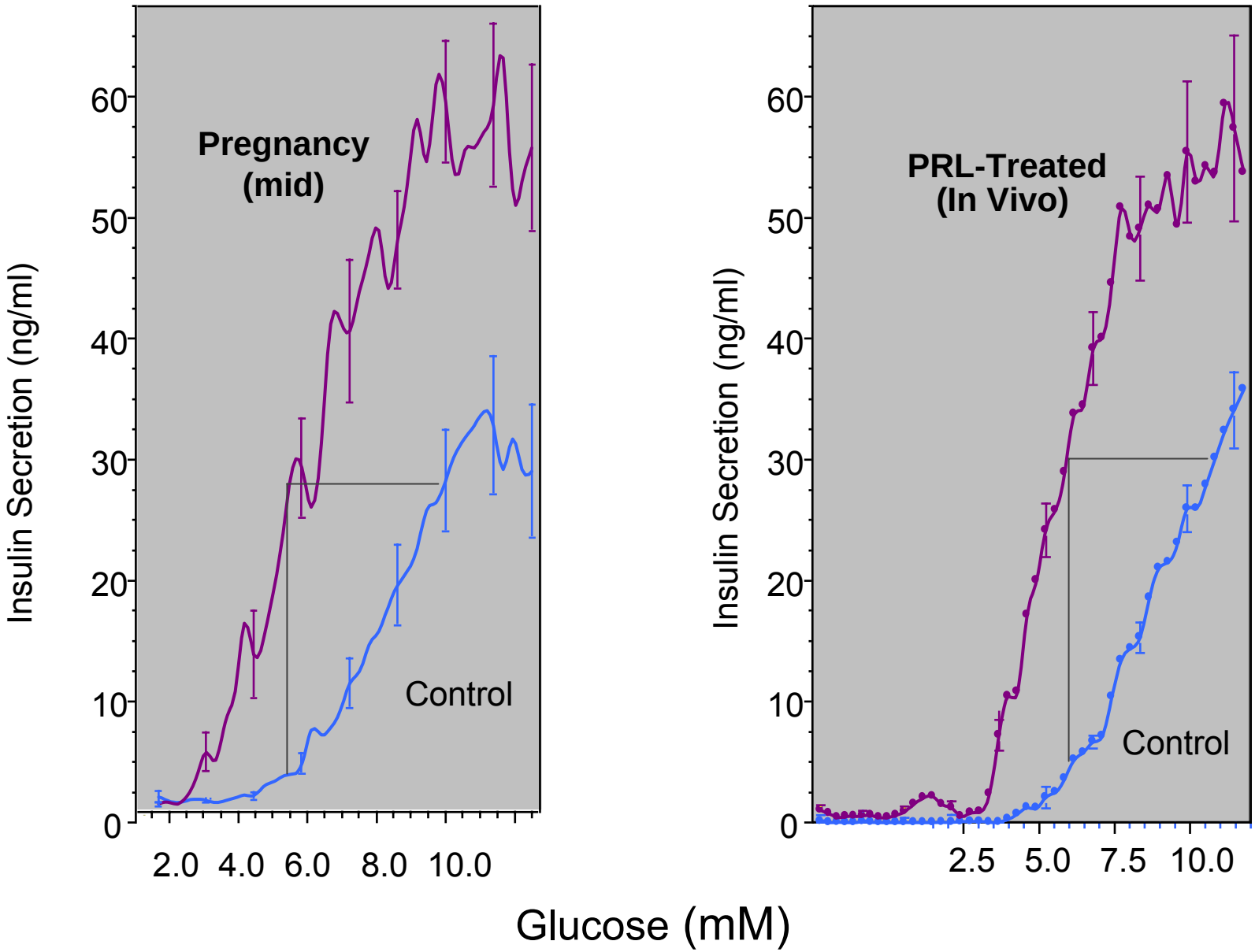




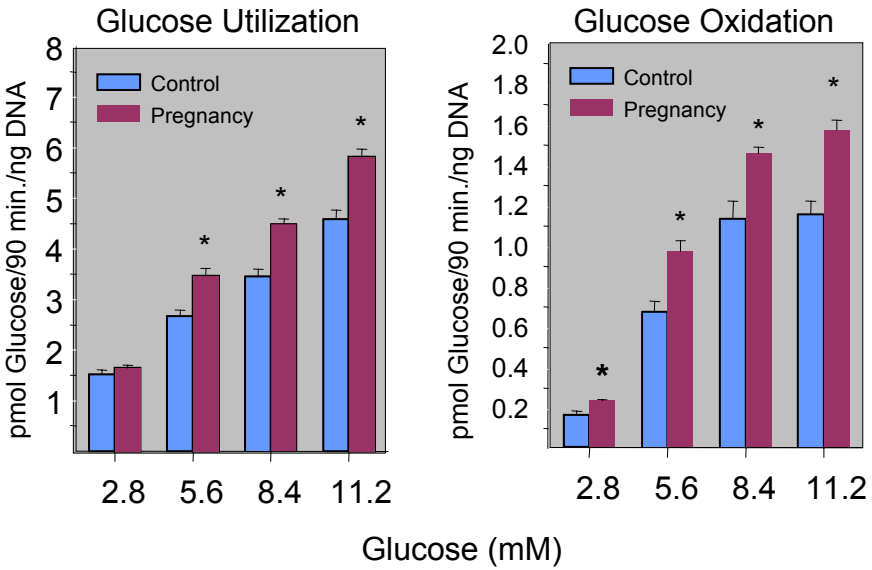
Lactogen (Pregnancy)
Regulation of Insulin Secretion

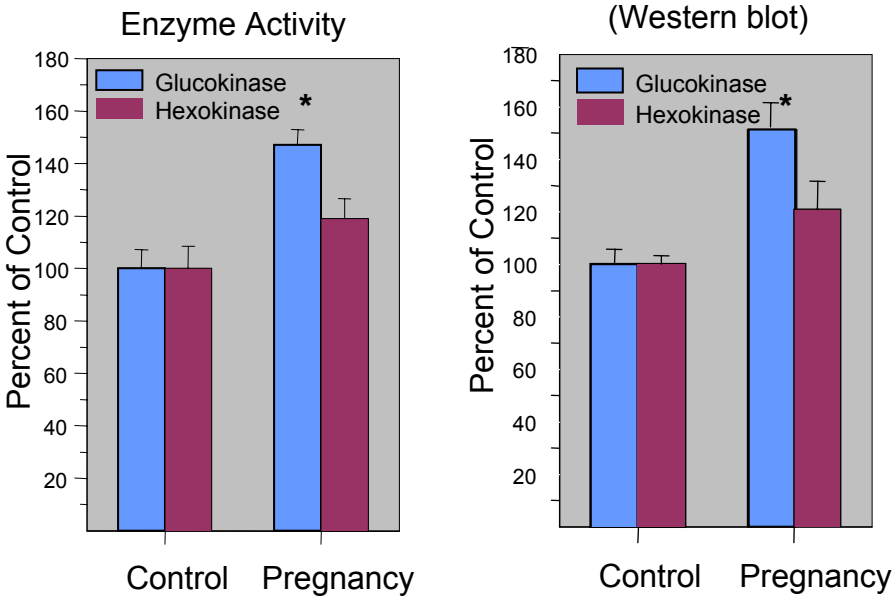
- Decreased threshold for glucose stimulated insulin secretion
- Enhanced insulin secretion at normal glucose levels
- Evidence for regulation of insulin secretion during pregnancy by way of the prolactin receptor

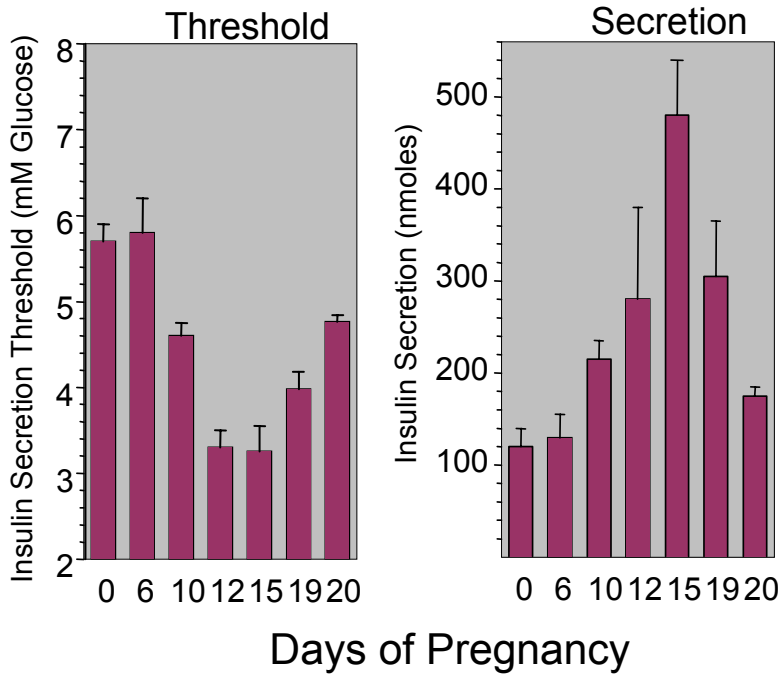
Effect of Pregnancy & Prolactin on
Glucose Stimulated Insulin Secretion



Effect of Pregnancy on Glucose metabolism and Insulin Secretion



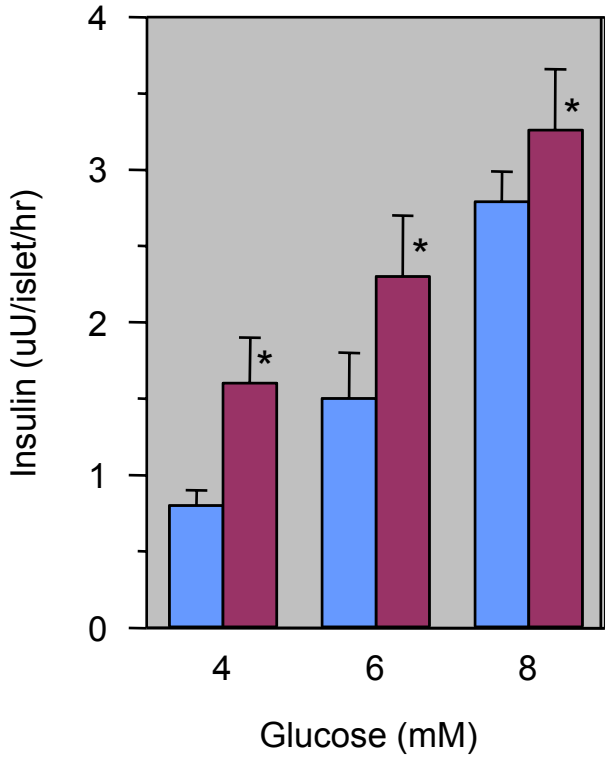




Effect of PRL with '0' glucose on Islets

Culture 2 days in 0 mM Glucose → Stimulate 1hr in 4 - 8 mM Glucose → Assays and Western

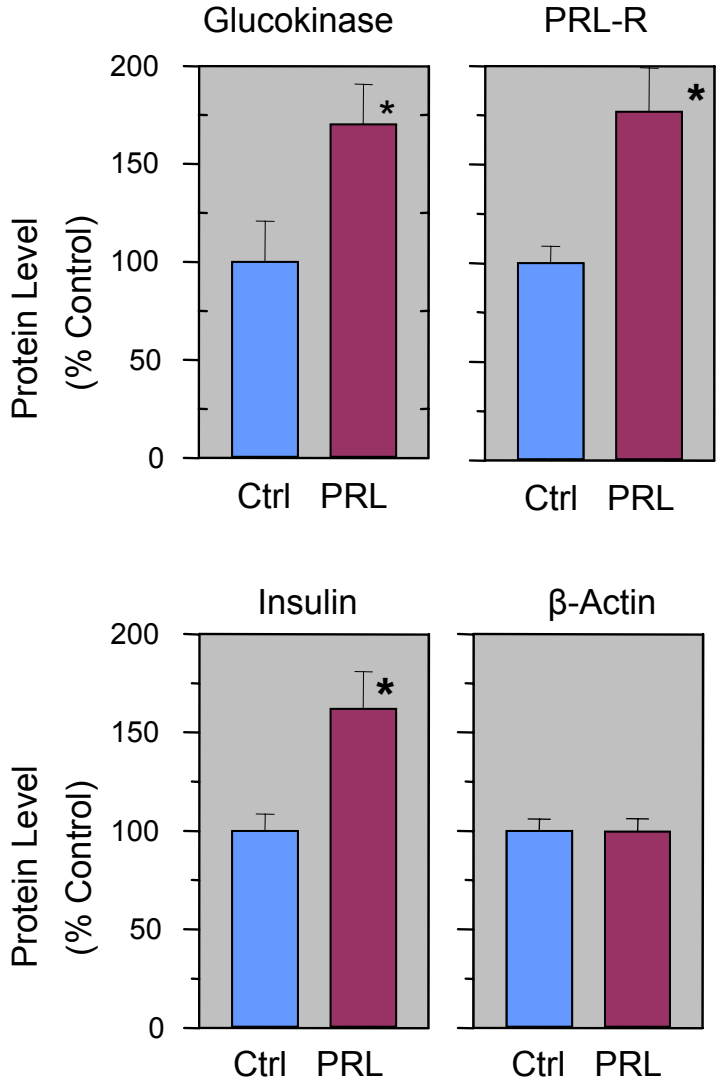
Insulin Secretion

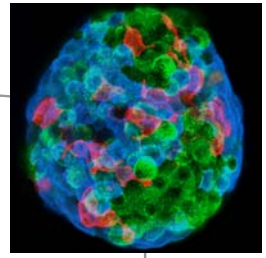


Control

Prolactin

Western Analysis





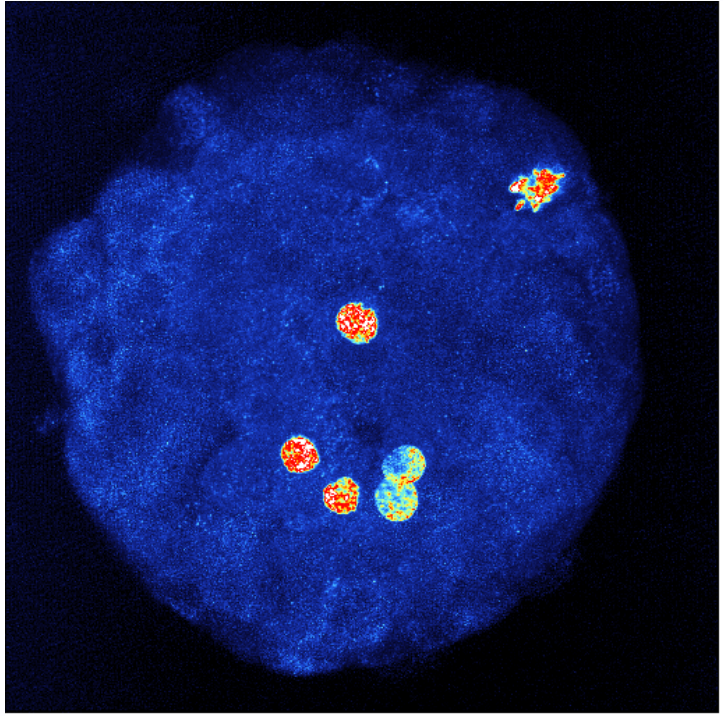
Lactogen (Pregnancy)
Regulation of β-cell Growth

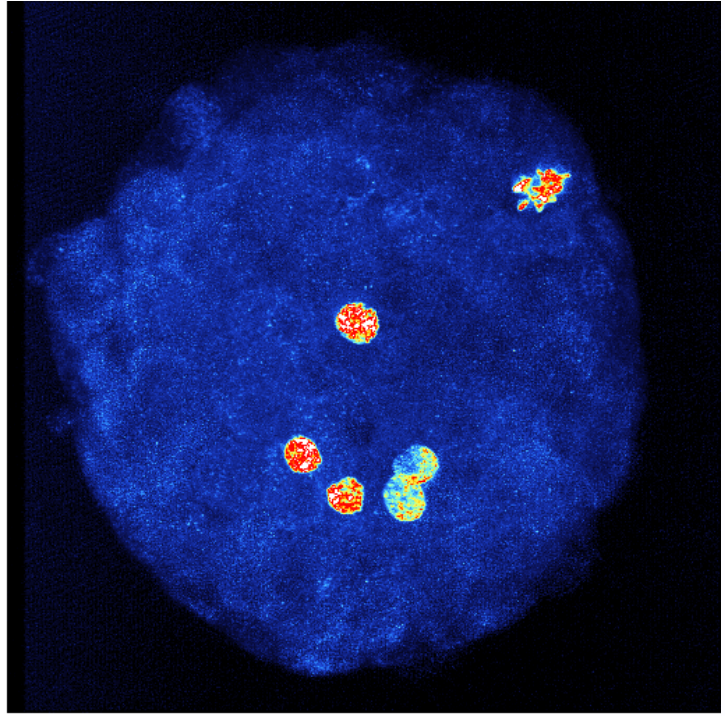
- β-cell growth during pregnancy
- Effect of prolactin and placental lactogen on β-cell growth
- Pulsed versus continuous stimulation by prolactin
- Islet mass and numbers during pregnancy
- β-cell size
- Role of prolactin regulation of cyclin D
- Comparison of prolactin to other β-cell growth factors

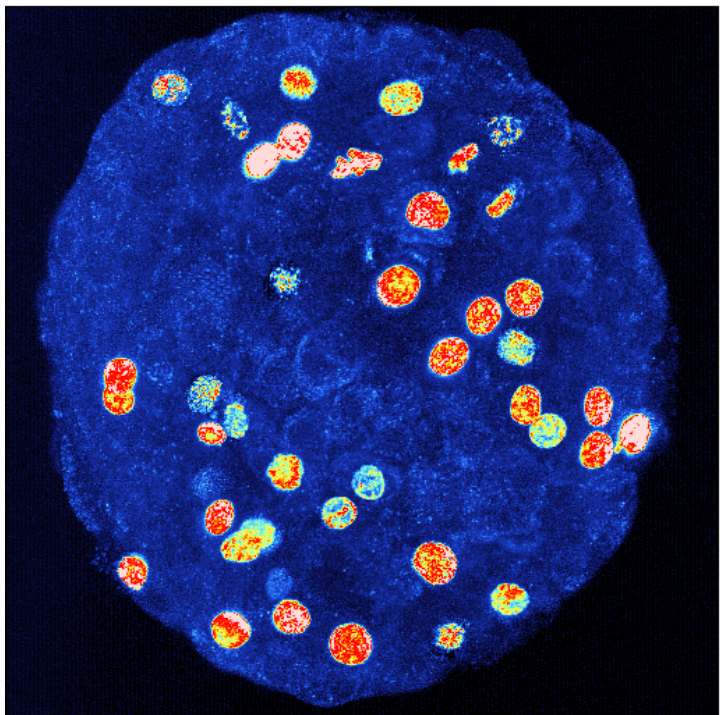
BrdU Labeled Nuclei in Islets

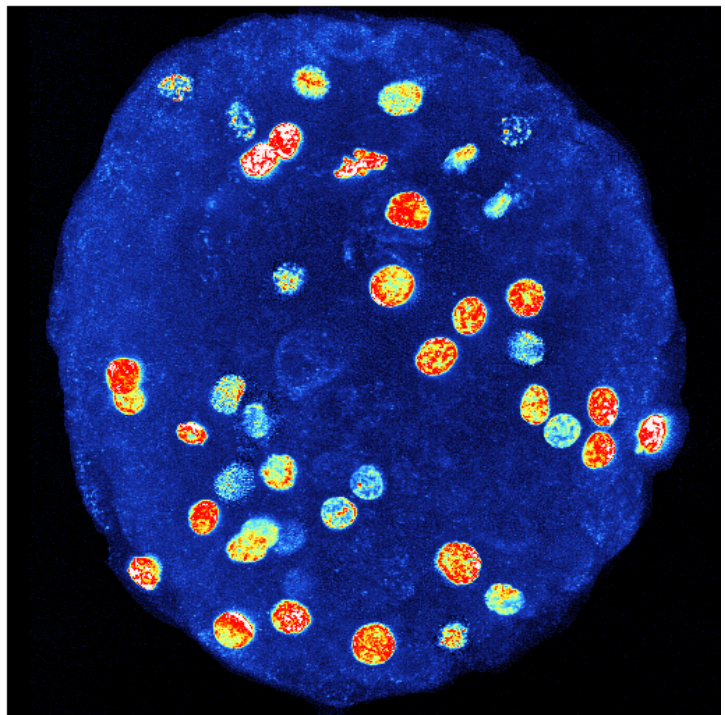
Control

Placental Lactogen





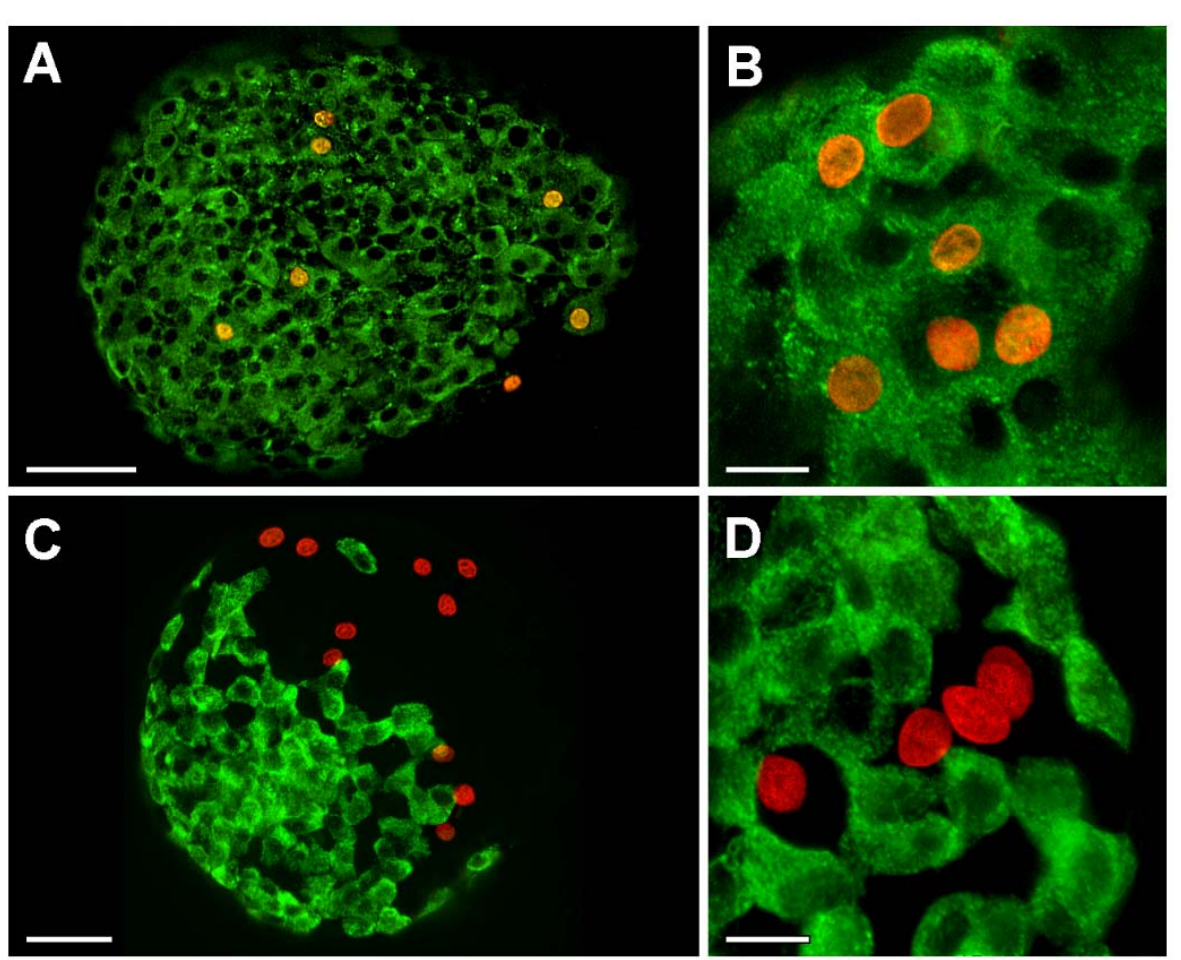




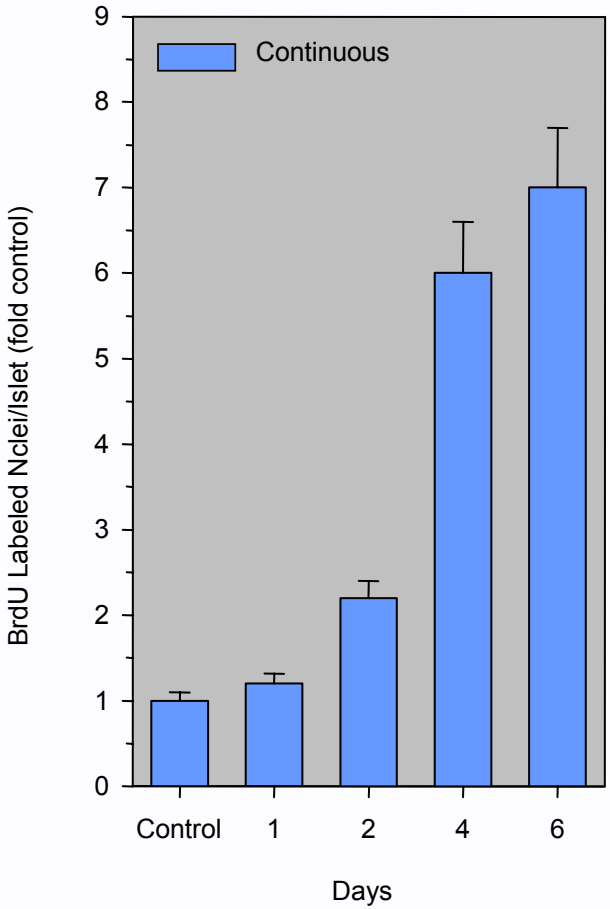
BrdU Labeled Nuclei in Islets

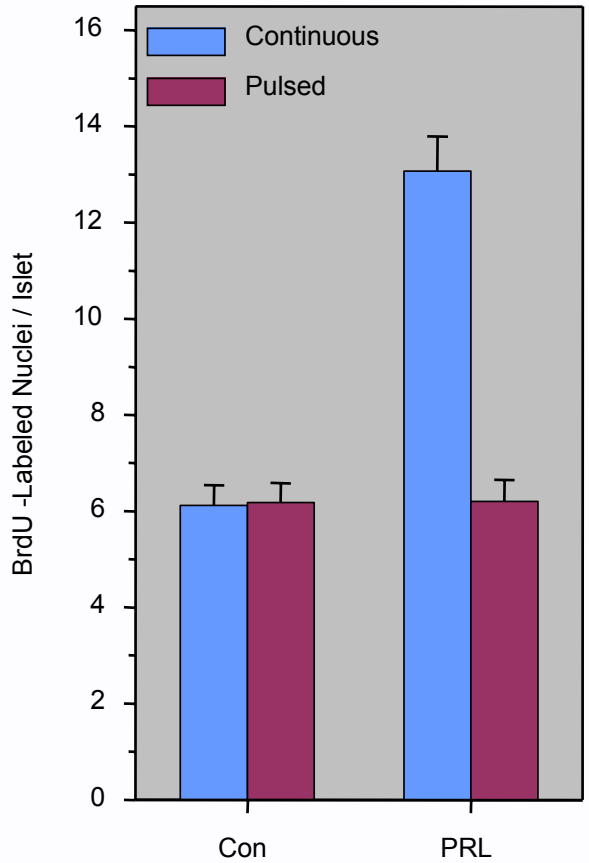
Insulin

Glucagon

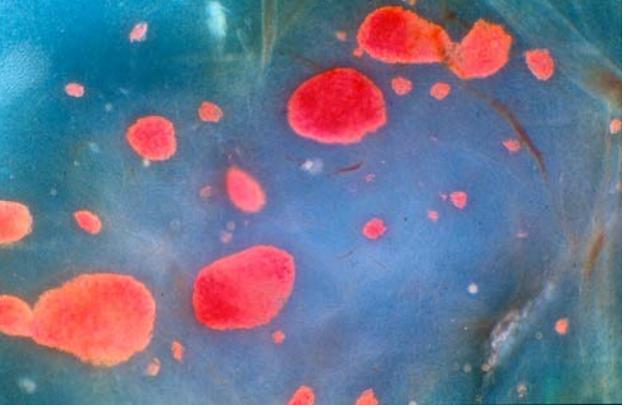


Effect of Prolactin (continuous vs. pulsed) on BrdU Incorporation into Islets

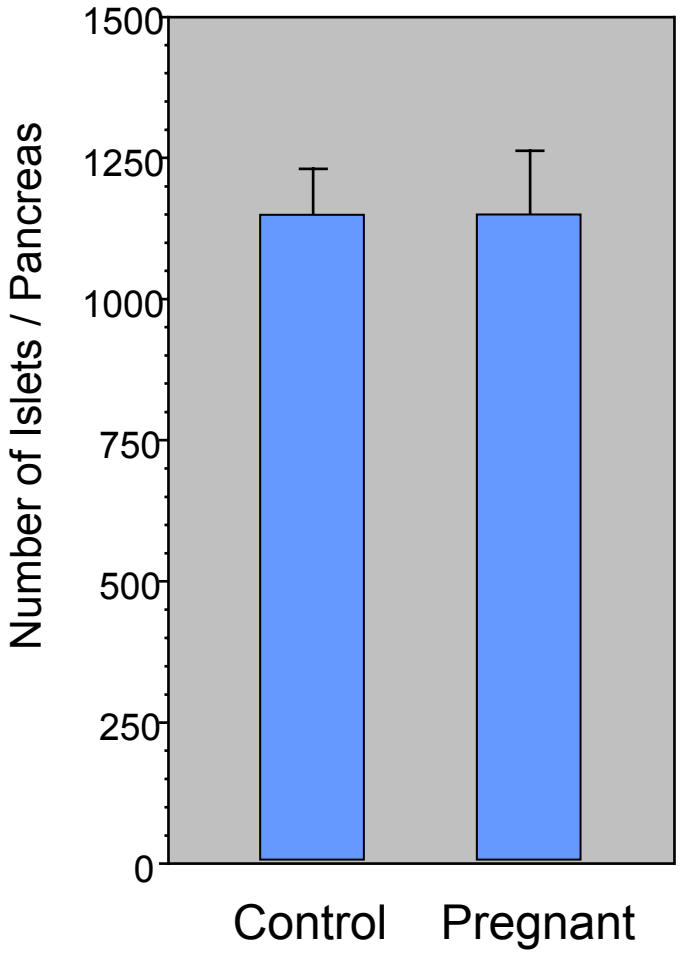


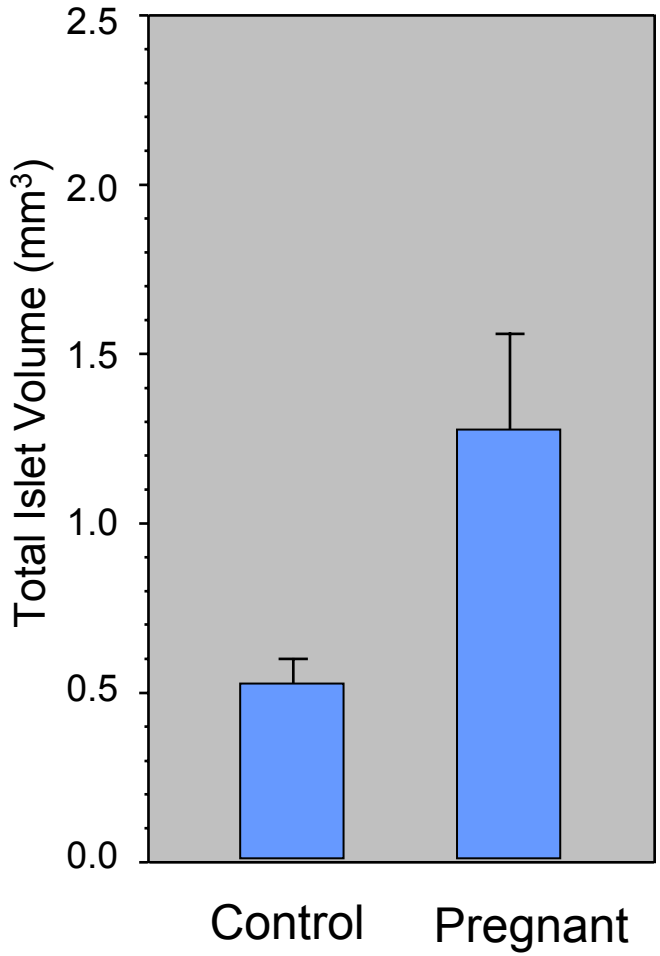


48 hour experiment:
pulsed treatment for 1 hour
every 4 hours.



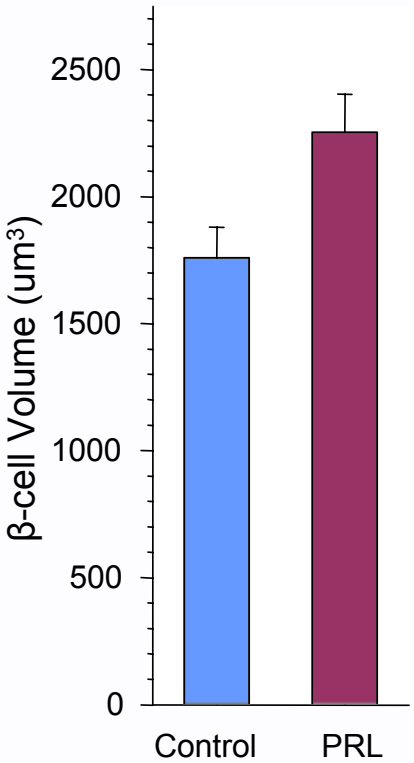
Number of Islets and Islet Volume in Pregnant Mice

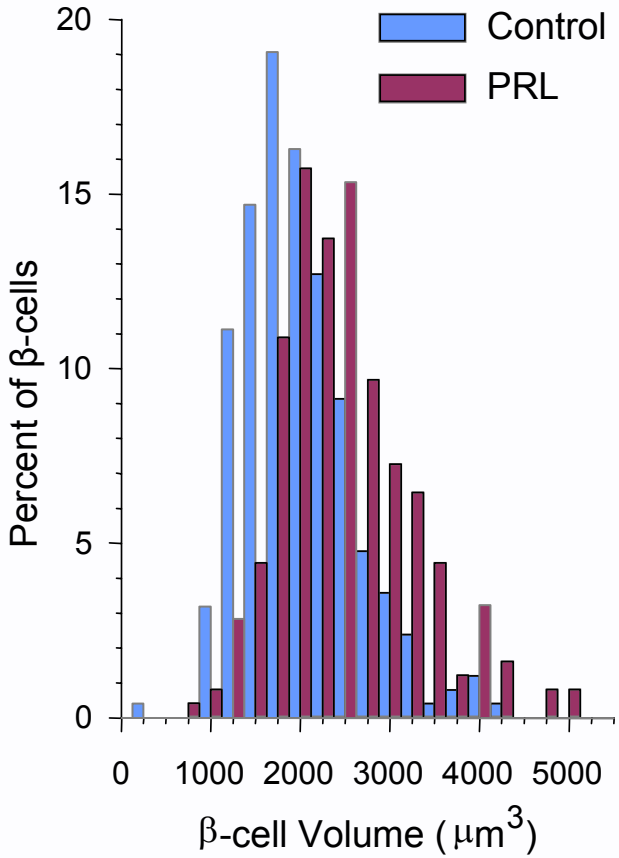




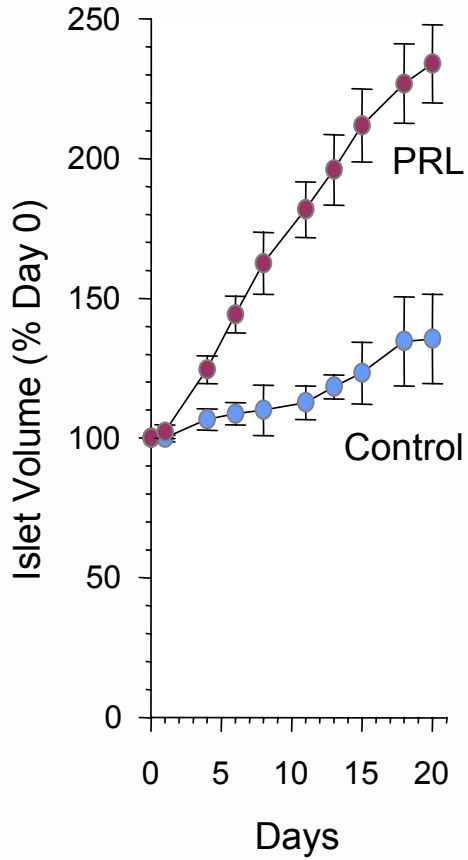
Effect of Prolactin on β-cell Size in Islets

β-cell Size Measured in Islets after 7 days

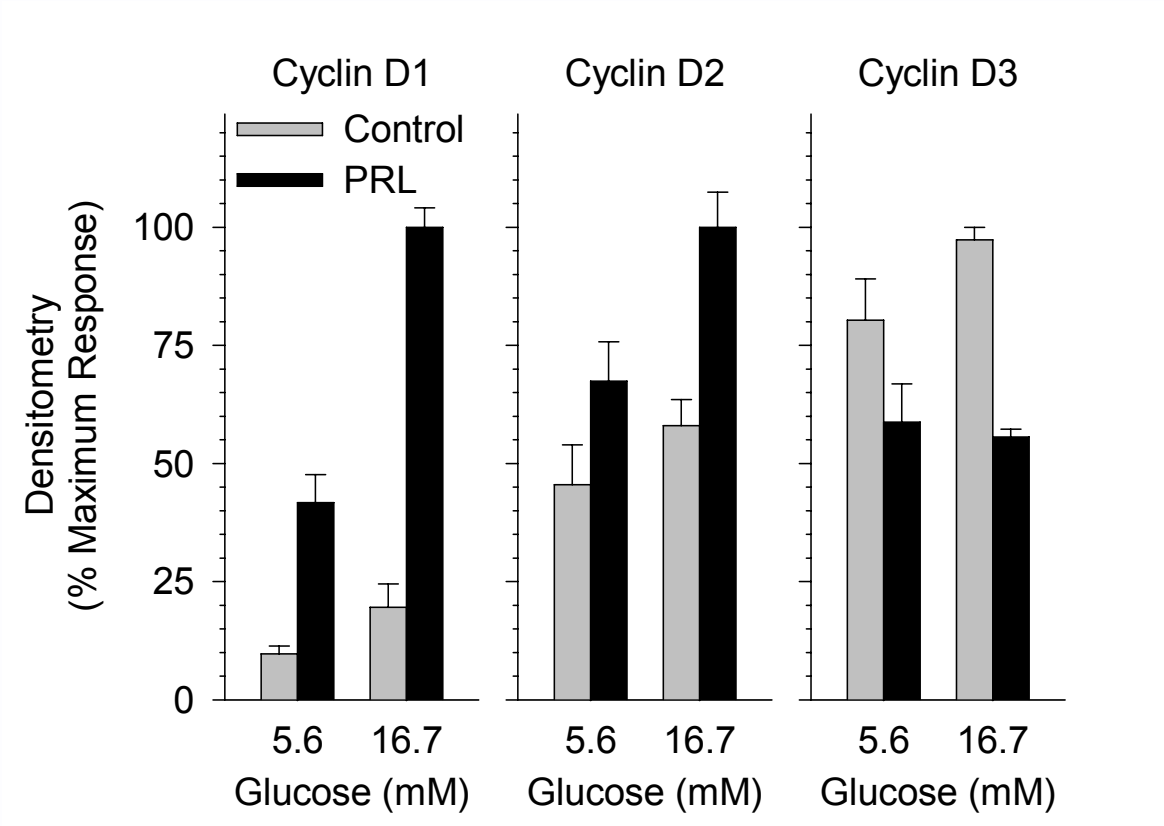




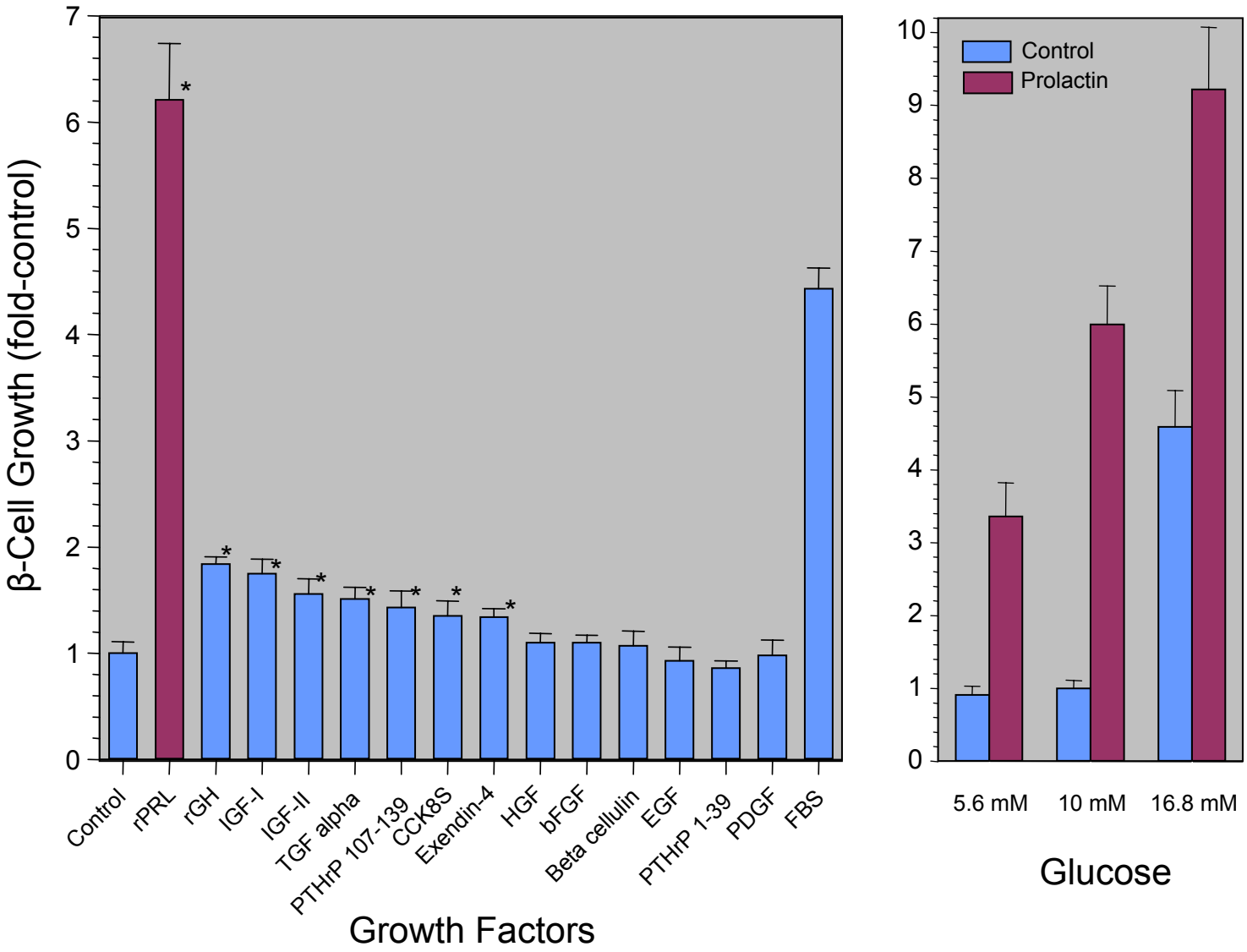
Change in Volume of Individual Islets



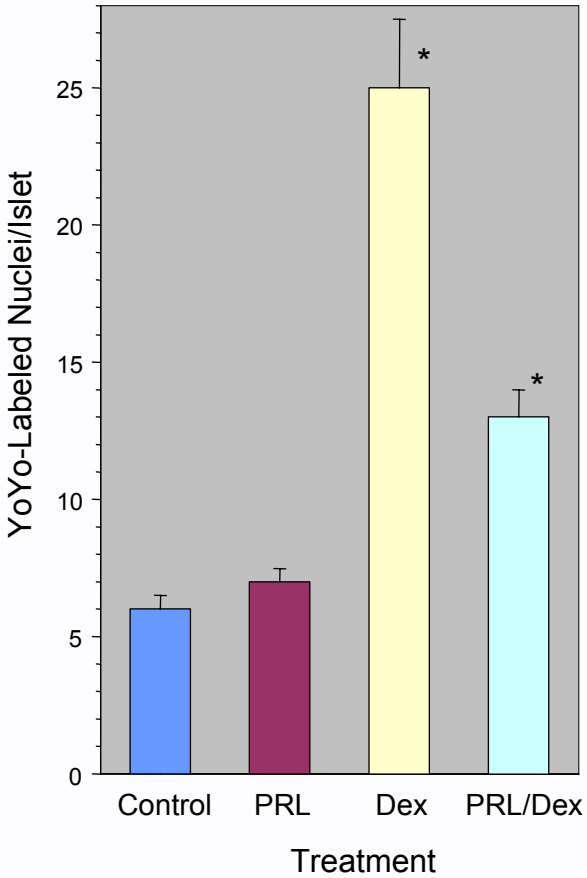
Effect of Prolactin on Cyclin D Expression in INS-1 Cells (24 hr. treatment)

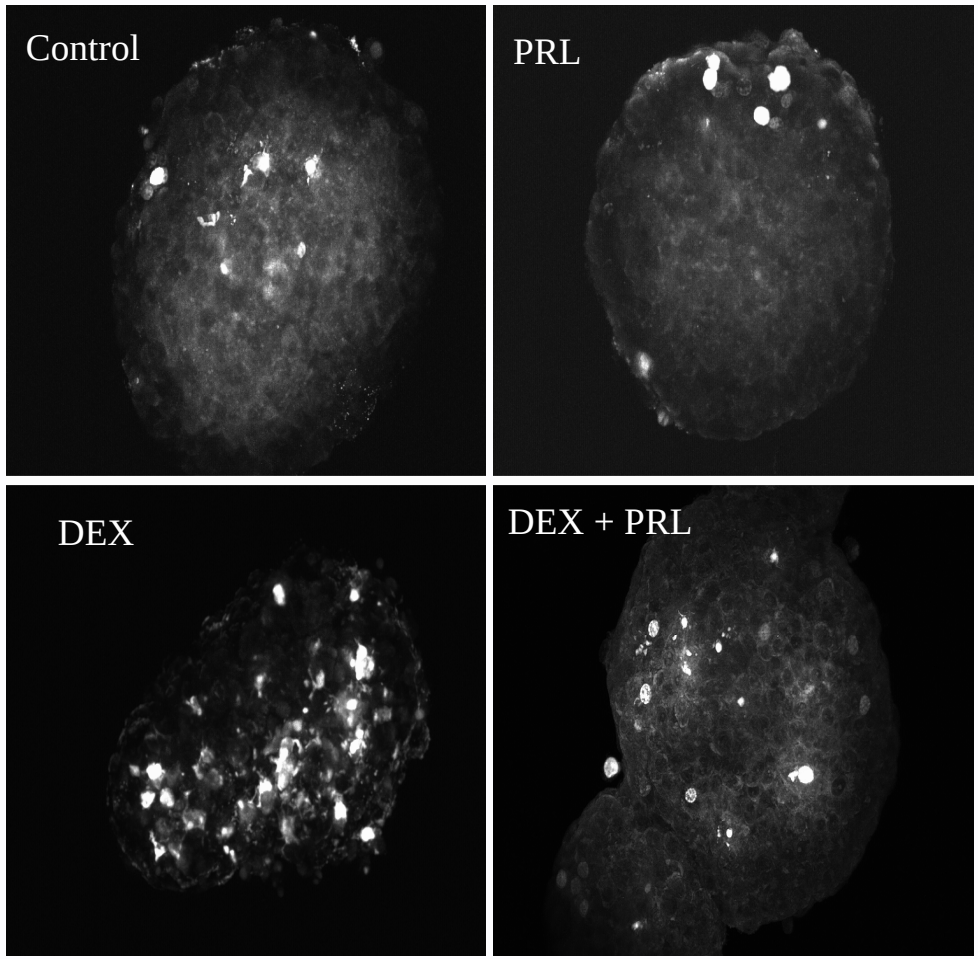


Hormonal Regulation of β-cell Growth in Islets



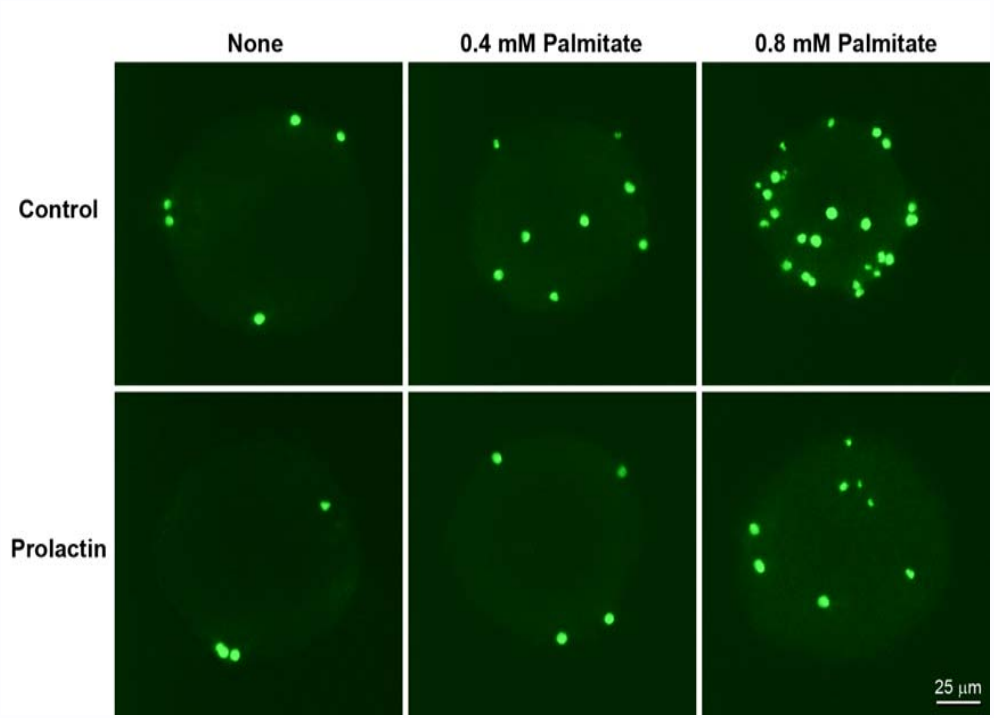
Effect of Dexamethasone and Prolactin on Islet Cell Death

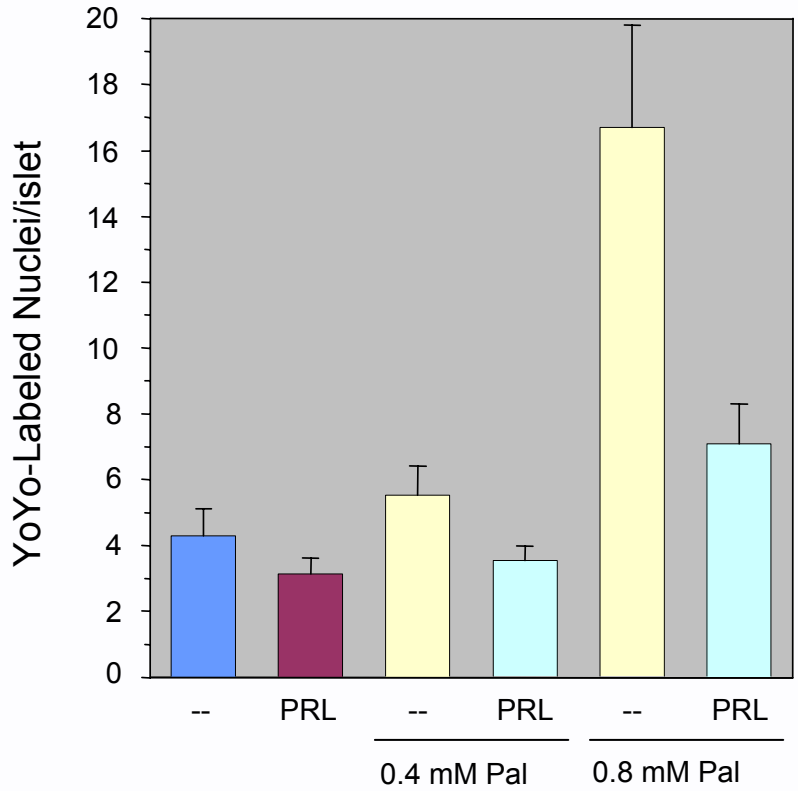




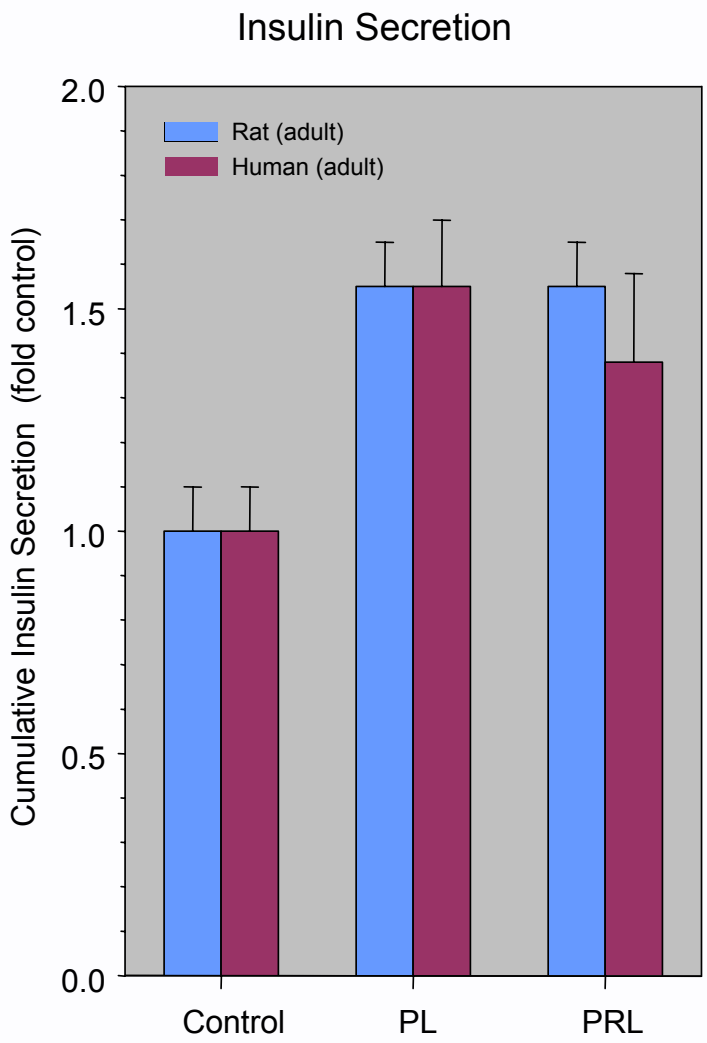
Dexamethasone 100 nM for 48 hours

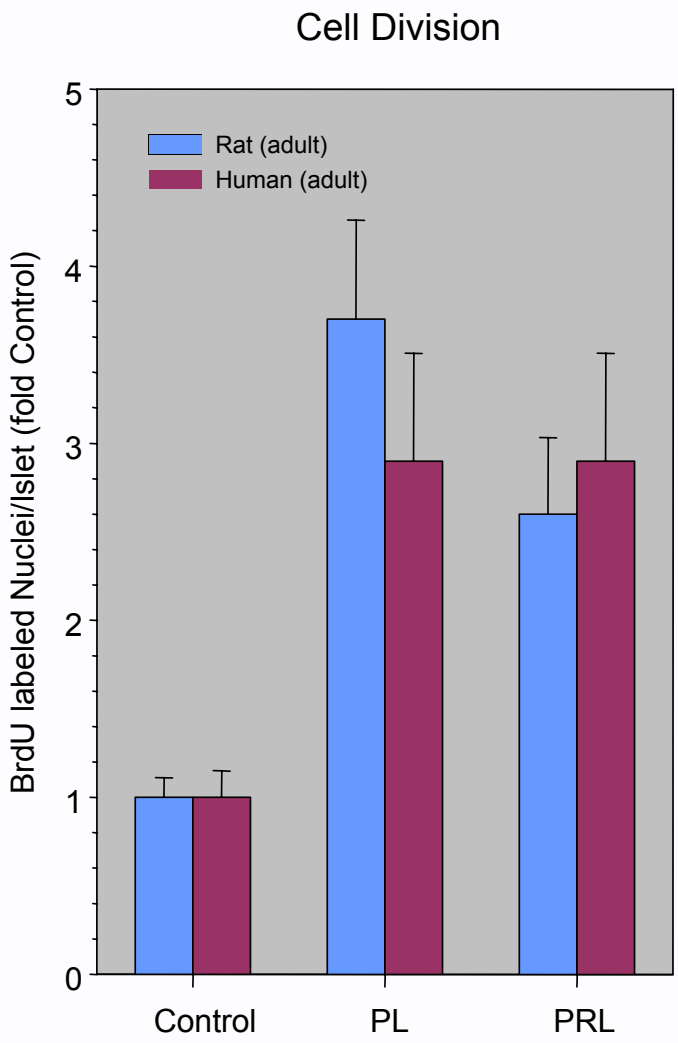
Effect of Prolactin and Palmitate on Islet Cell Death





Placental lactogen and Prolactin Regulation of Insulin Secretion and β-cell Growth in Adult Human islets and Adult Rat islets in vitro





Human β-cell Studies with Prolactin

1. Beneficial Effects of Prolactin and Laminin on Human Pancreatic Islet-cell Cultures:
   L. Labriola, W. Montor, K. Krogh, F. H. Lojudice,T. Genzini, A. C. Goldberg, F. G. Eliaschewitz, M. C. Sogayar, Molecular and Cellular Endocrinology 263 (2007) 120–133

   Treatment of primary human islet cells with human prolactin results in:

   – Increase in JAK-2 and Stat5 phosphorylation
   – 3-fold increase in islet cell proliferation
   – 3-fold increase in insulin content and RNA
   – 5-fold increase in insulin secretion

2. β-cell Specific cytoprotection by Prolactin on Human Islets: T. Yamamoto, C. Ricordi, A. Miki, Y. Sakuma, A. Mita, R.D. Molano, A. Fornoni, A. Pileggi, L. Inverardi and H. Ichii., Xenotransplantation 14 (2007) 457

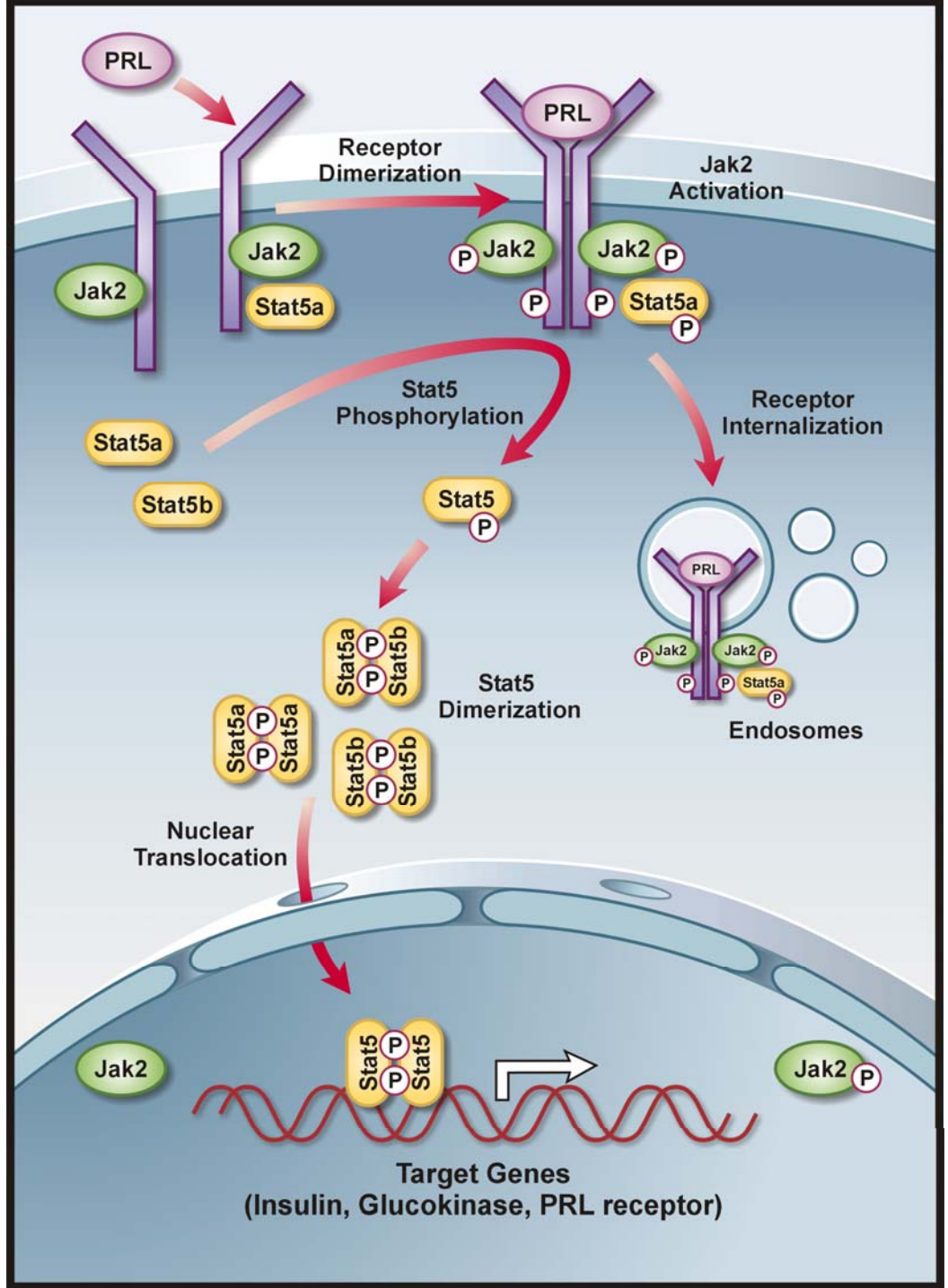
   Treatment of human islets with prolactin for 48 hours prior to treatment with noxious stimuli for 48 hours:

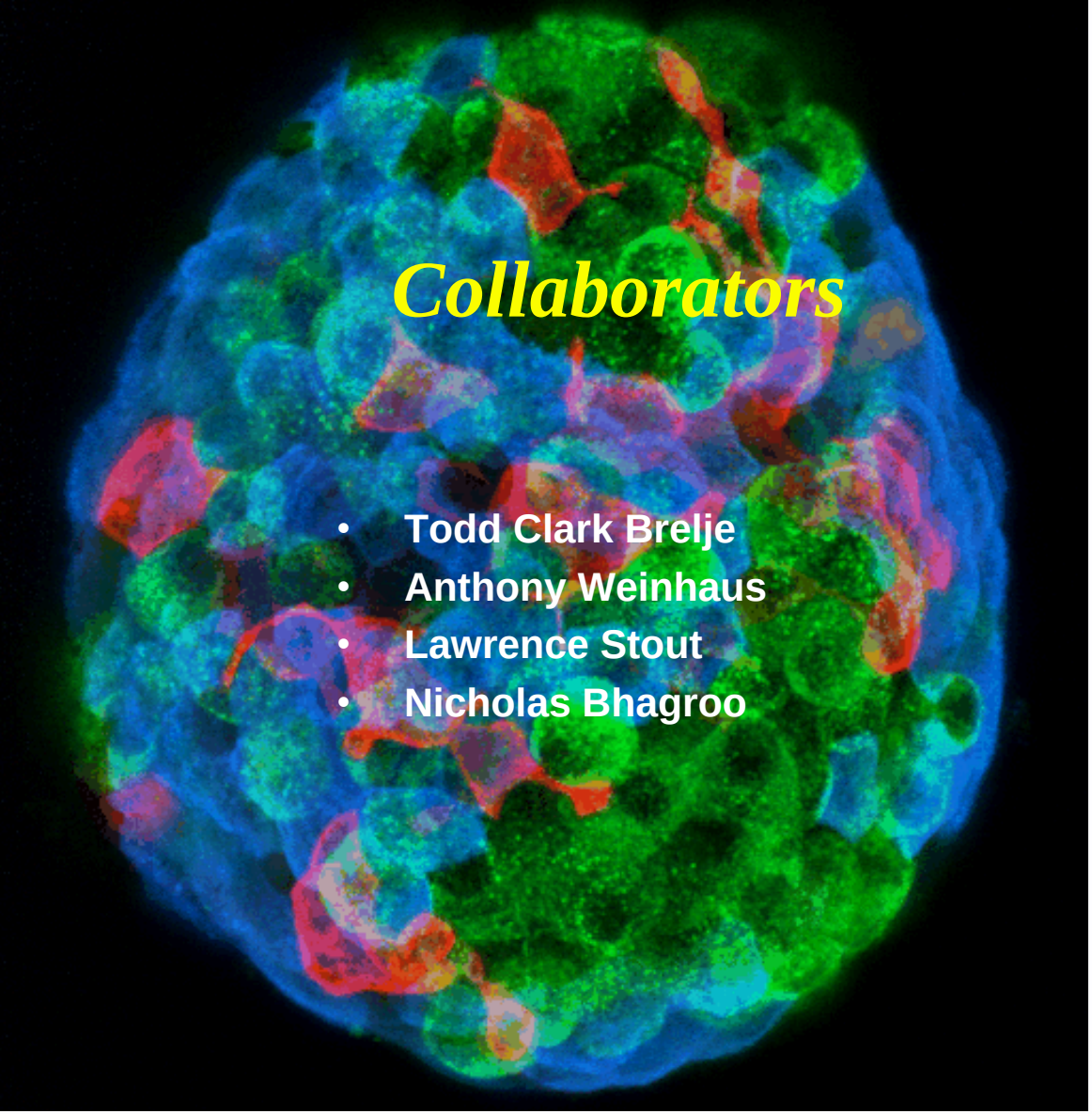
   – Prolactin showed significant protective effects against SNAP, h_20_2 and cytokines (IL-I-β, TNF-α and IFN-γ), but not hypoxia.
   – Relative islet β-cell content increased 19%
   – Relative viable β-cell mass incrased 28%

3. Others

Summary Effects of Prolactin Receptor Activation

- Increased glucose sensitivity
  - Glucokinase
  - Glucose oxidation
- Increased insulin secretion and insulin content
- Increased β-cell division
- Increased β-cell size
- Anti-apoptotic





Collaborators

- **Todd Clark Brelje**
- **Anthony Weinhaus**
- **Lawrence Stout**
- **Nicholas Bhagroo**

Brelje, T.C., M.W. Wessendorf and R.L. Sorenson 1993 Multi-color laser scanning confocal immunofluorescence microscopy: Practical application and limitations. Methods in Cell Biology. 38:98-193.