The regulation of insulin secretion through adipokines

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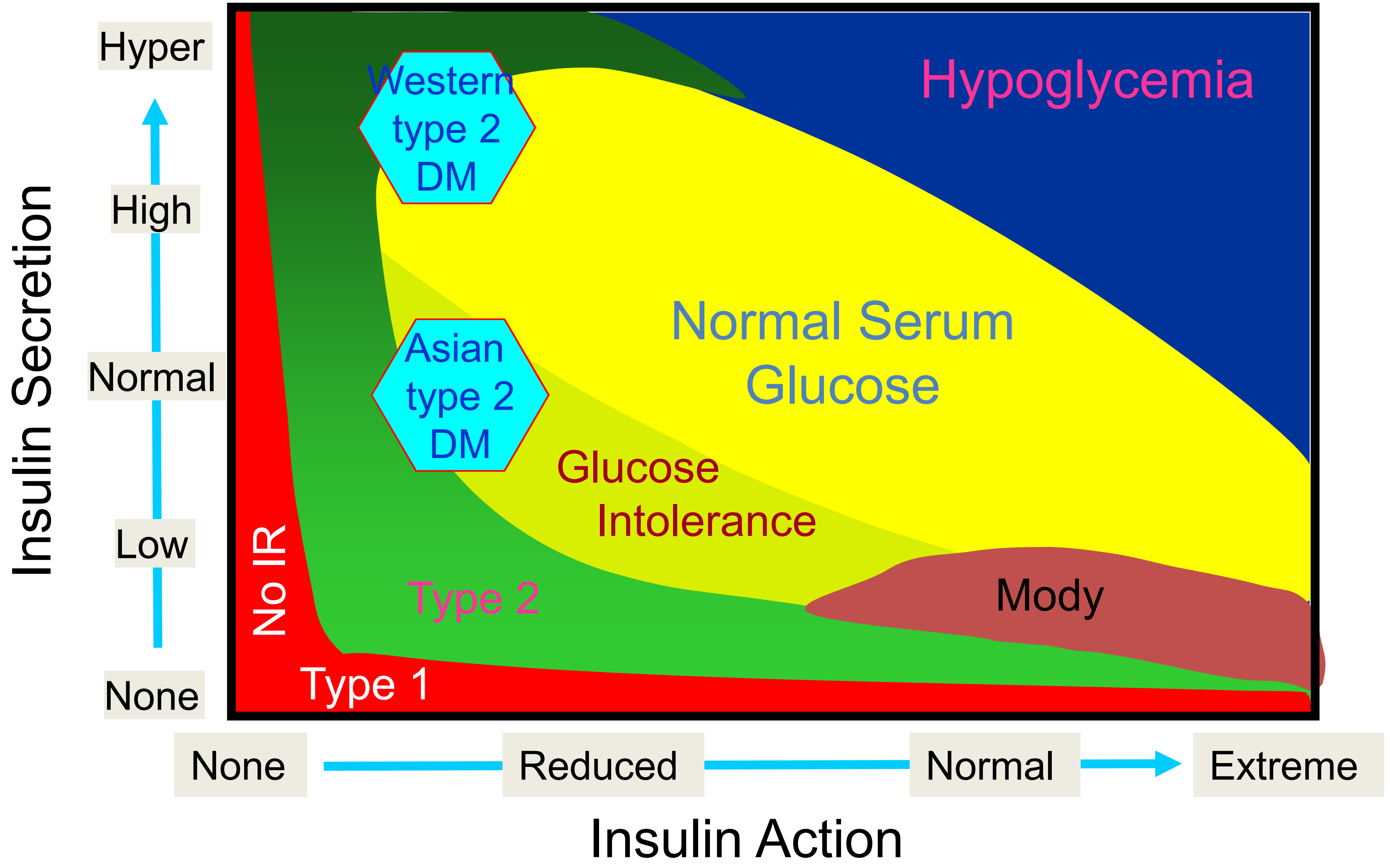
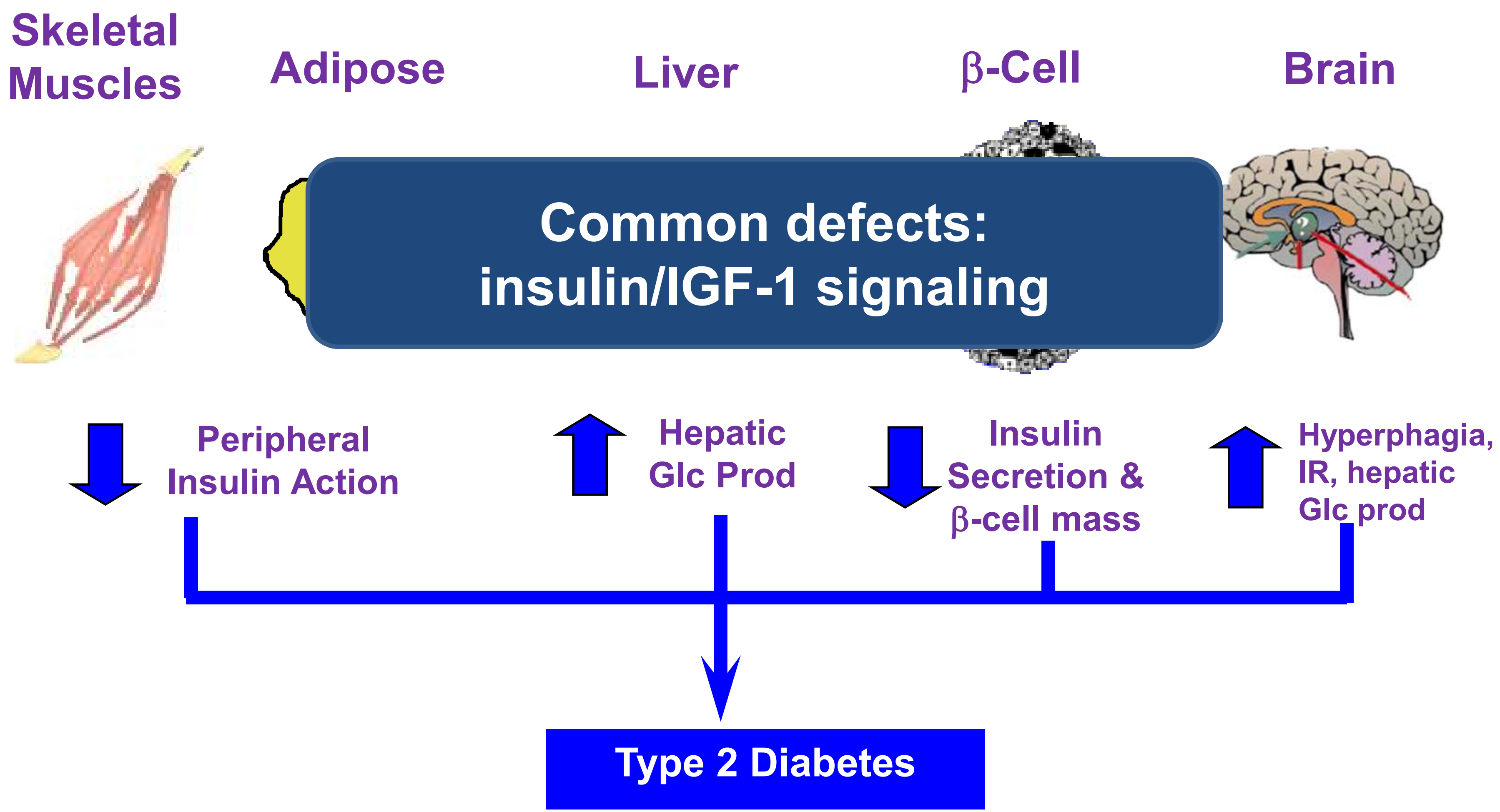
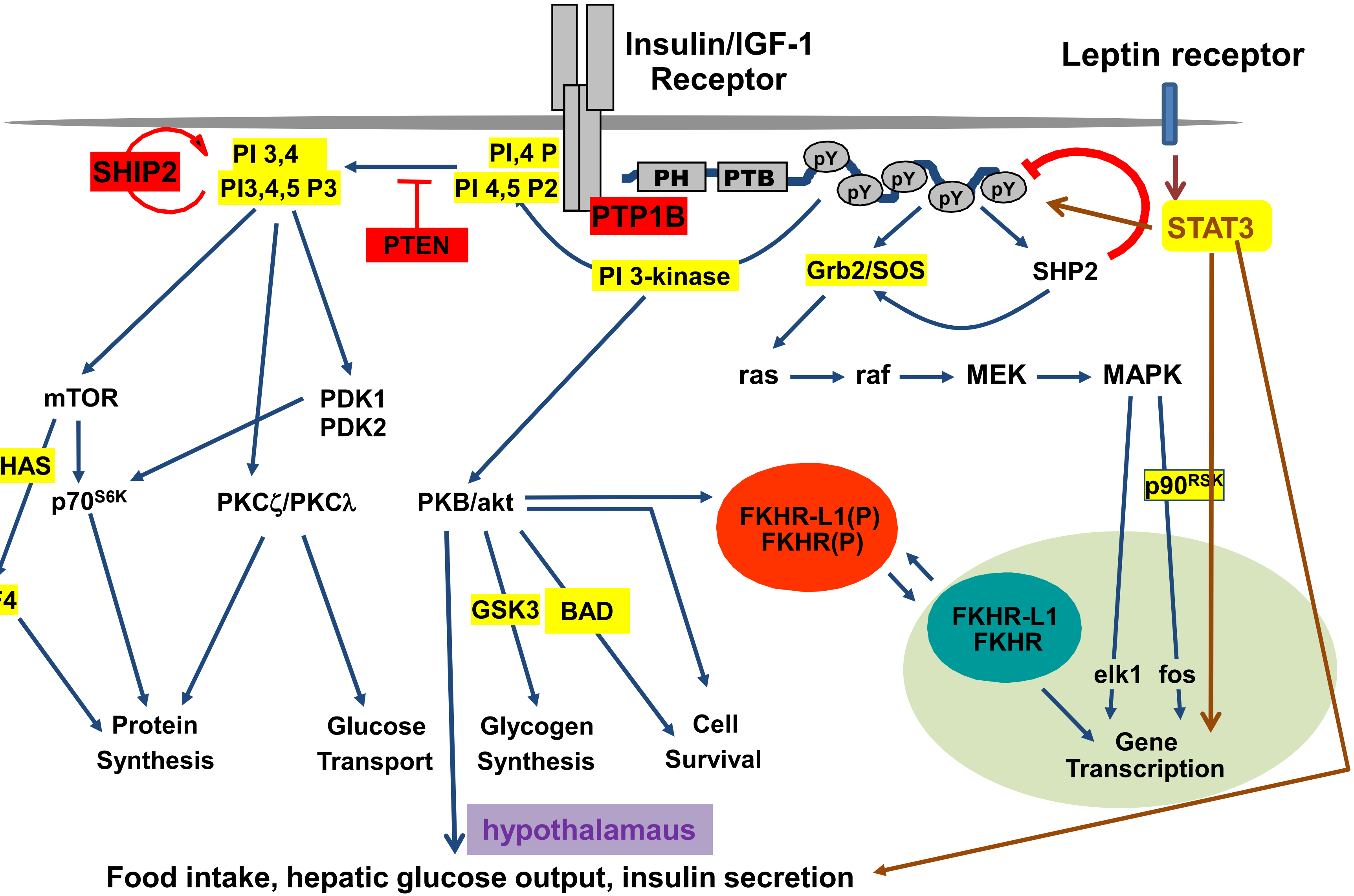
Relationship of insulin action and insulin secretion in type 2 diabetes



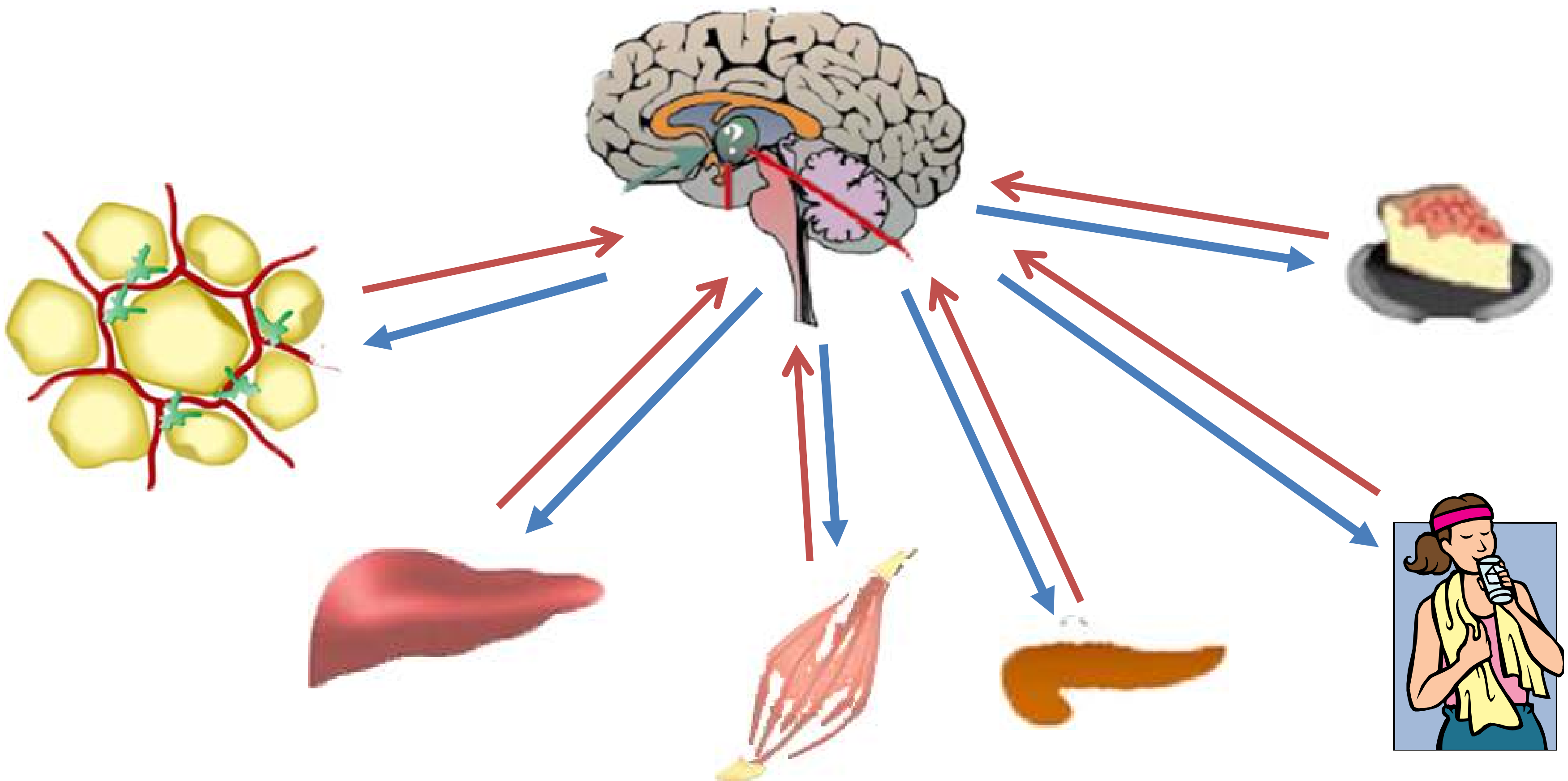
Type 2 diabetes results from Multi-system defects



Insulin/IGF-1 and leptin signaling



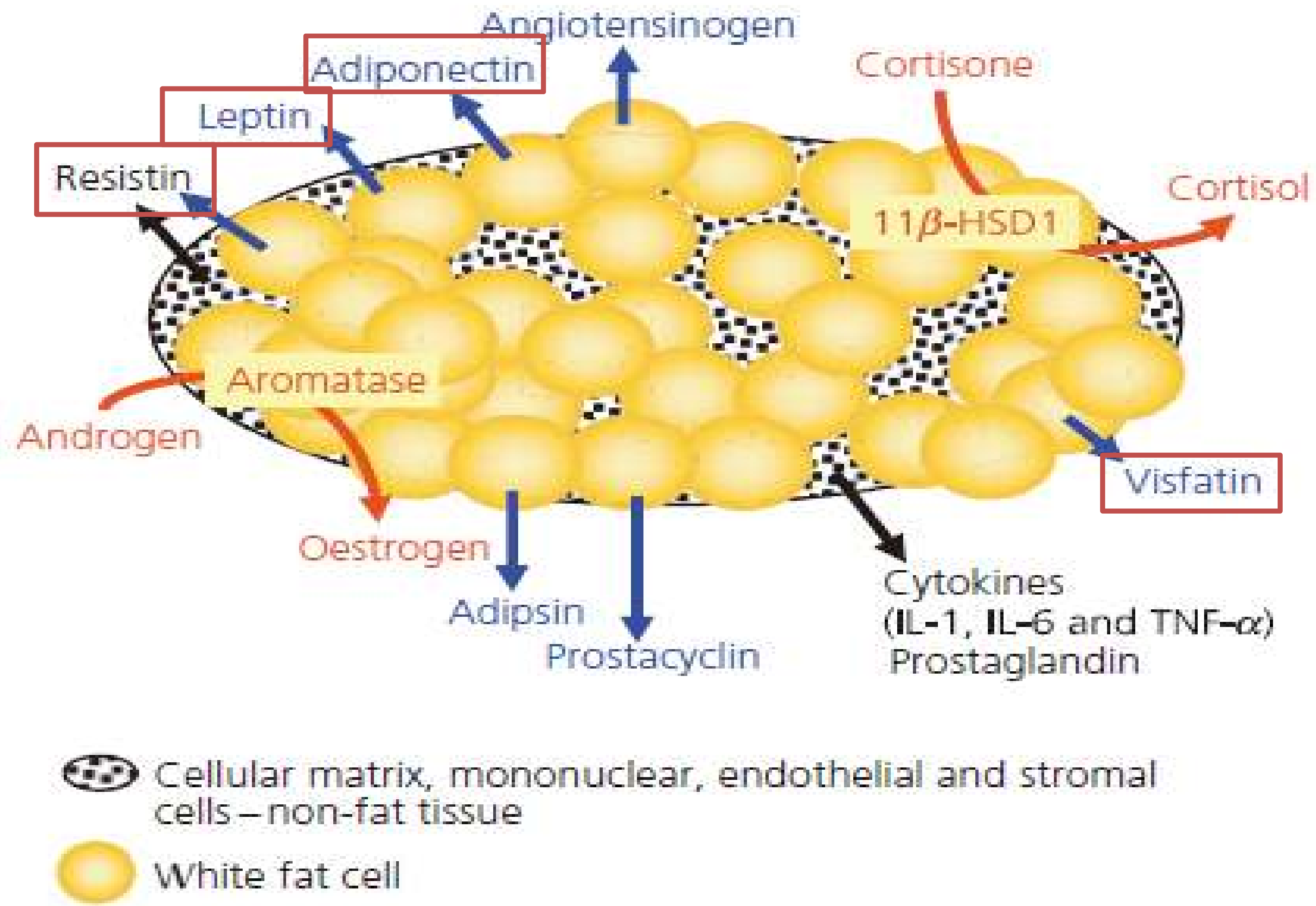
Regulate energy and glucose homeostasis in peripheral tissues through brain



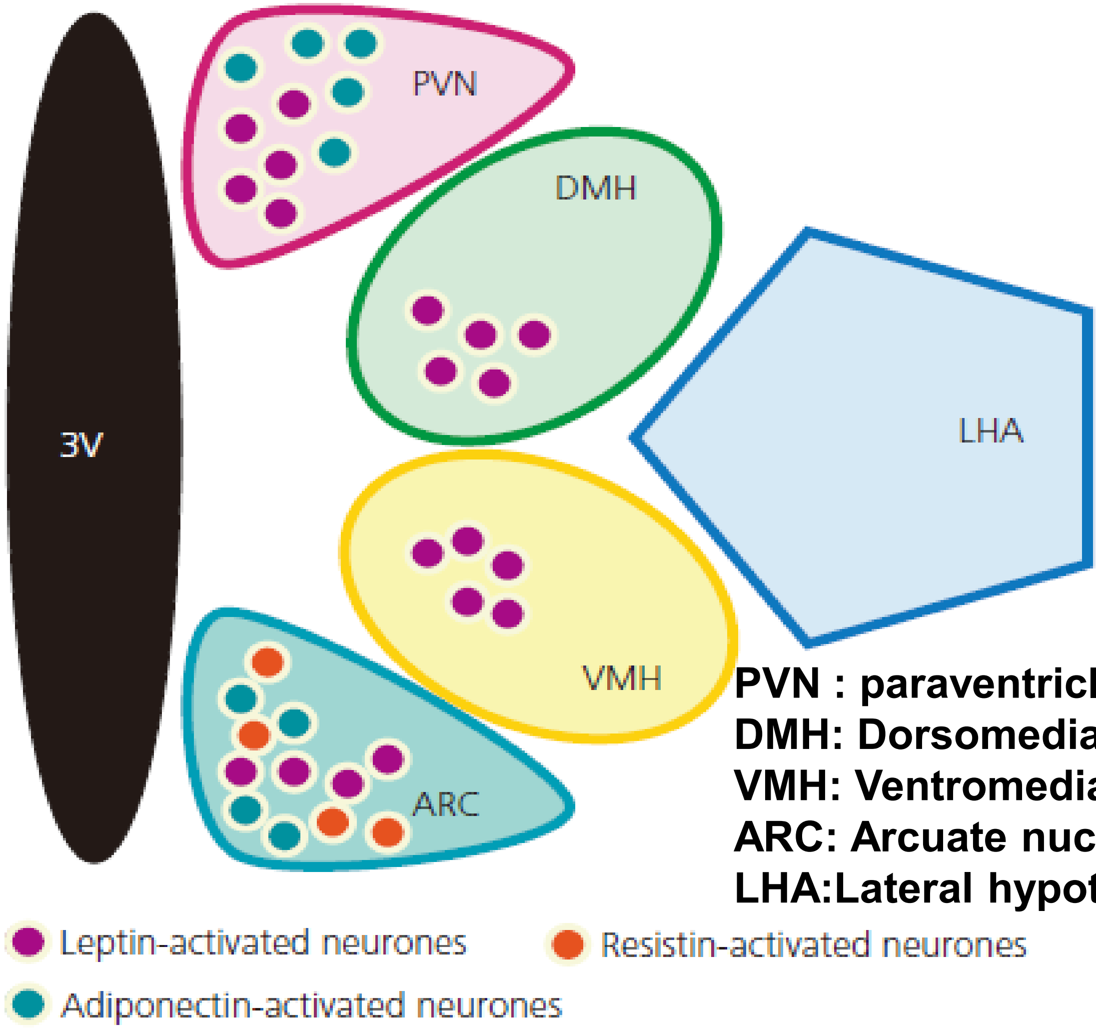
Autonomous nerve system and neurotransmitters

Adipokines, gut hormones, insulin

Adipokines secreted from white adipose tissues

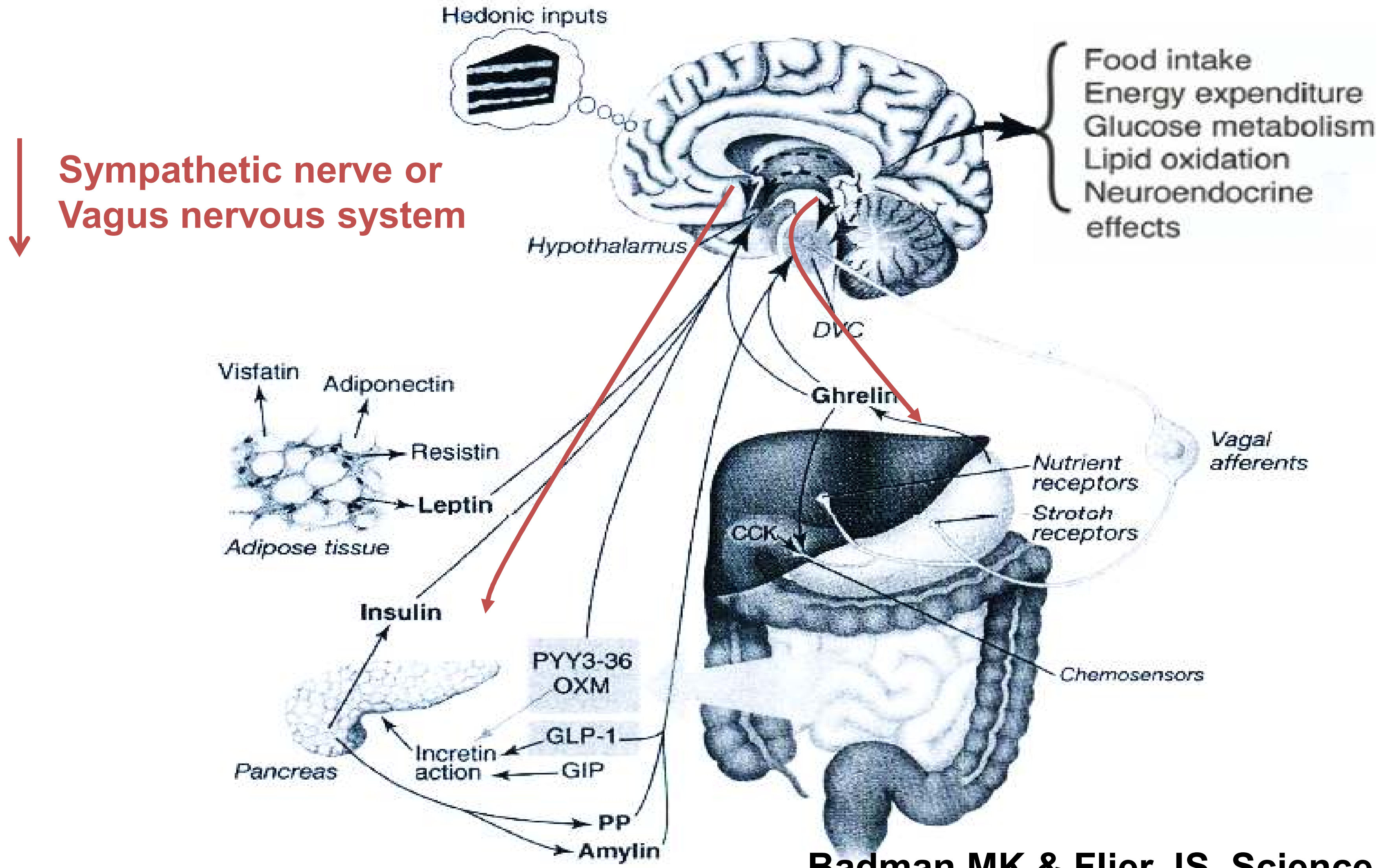


Adipokine neurons distributed in the hypothalamus



PVN : paraventriclular nucleus
DMH: Dorsomedial hypothalamic nucleus
VMH: Ventromedial nucleus
ARC: Arcuate nucleus
LHA:Lateral hypothalamic area

Long-term energy balance via brain

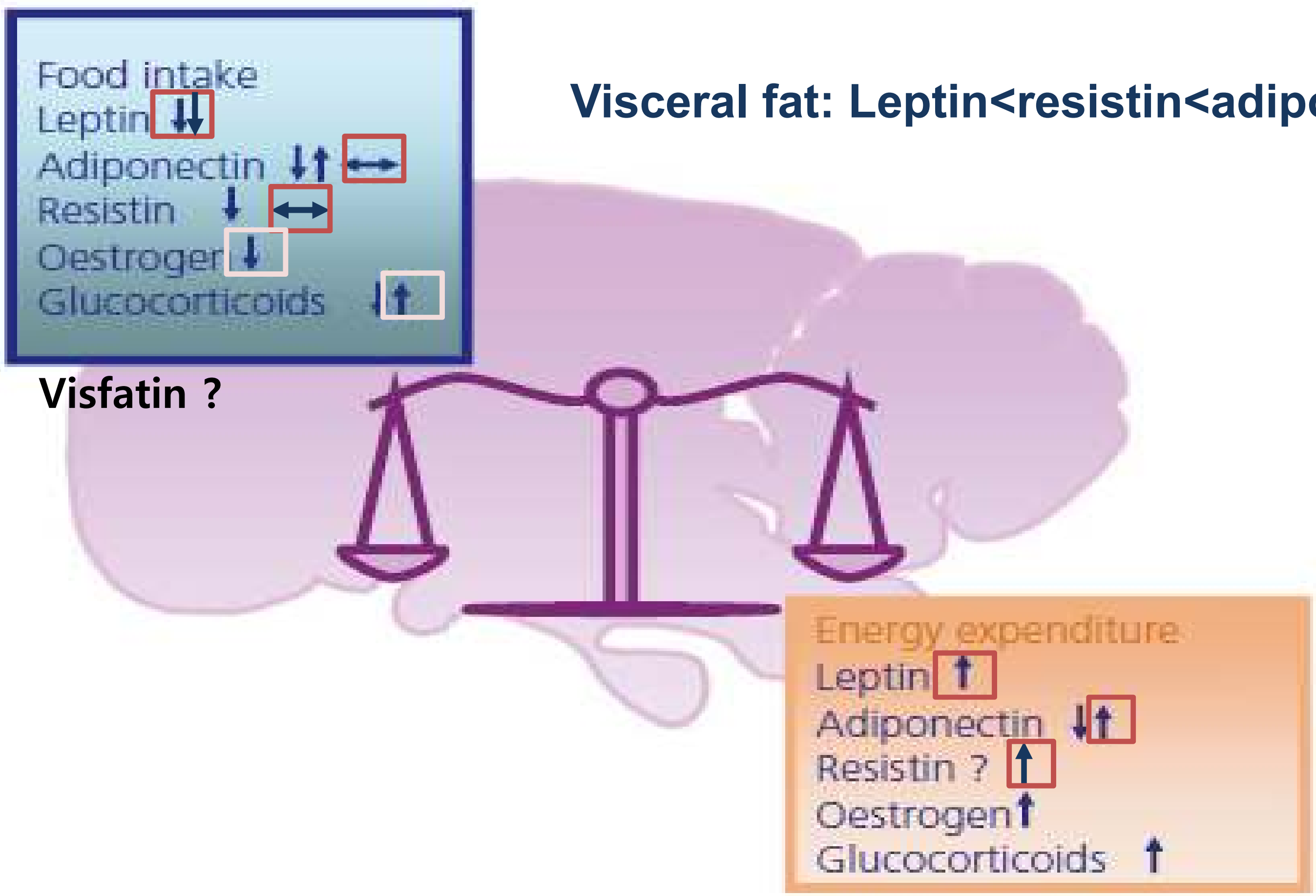


Badman MK & Flier JS. Science, 2005

Roles of adipokines
: energy homeostasis

ICV injection

IP injection



Visfatin ?

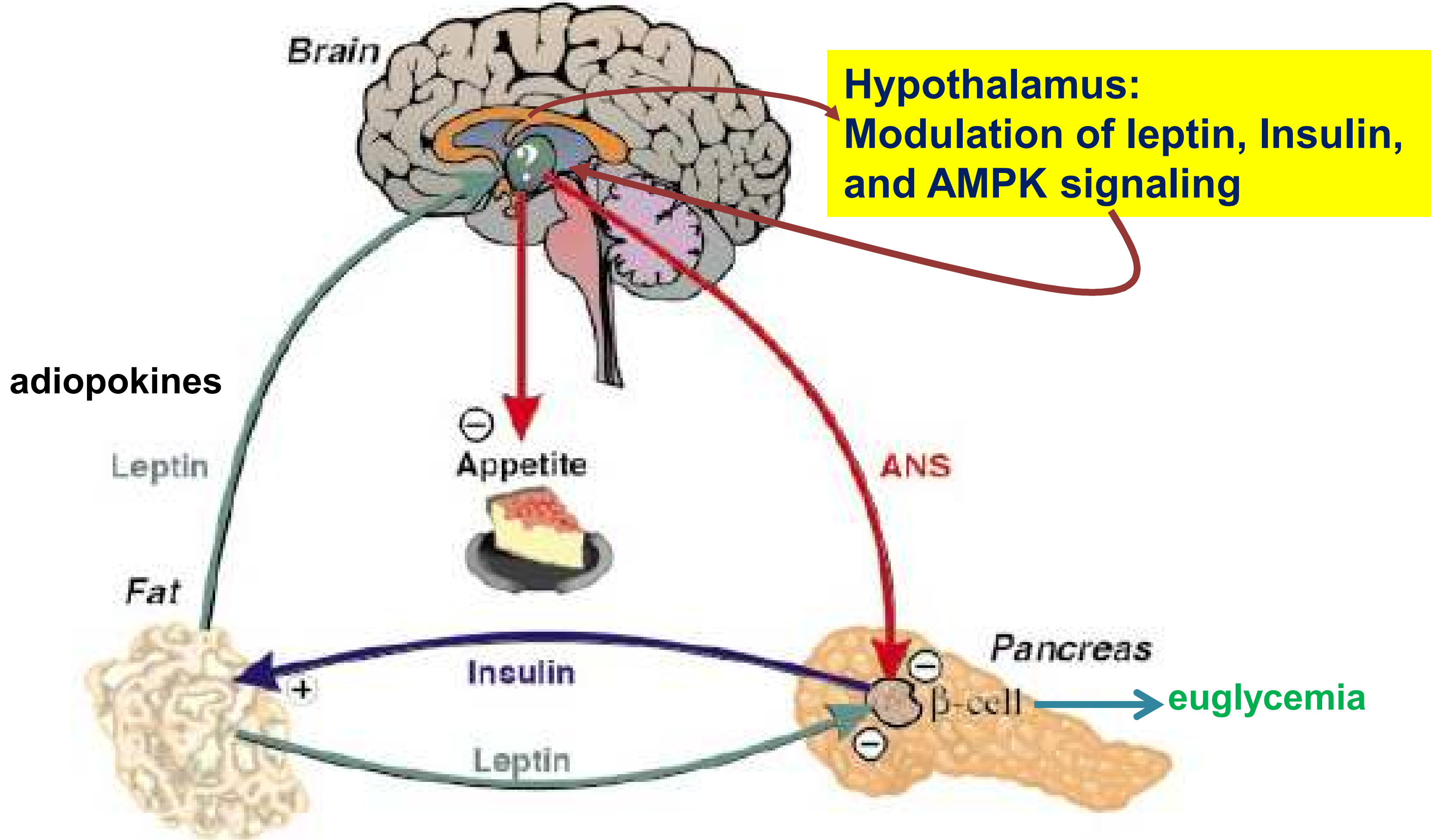
Visceral fat: Leptin<resistin<adiponectin

Visfatin ?

How do adipocytes interact with islets?

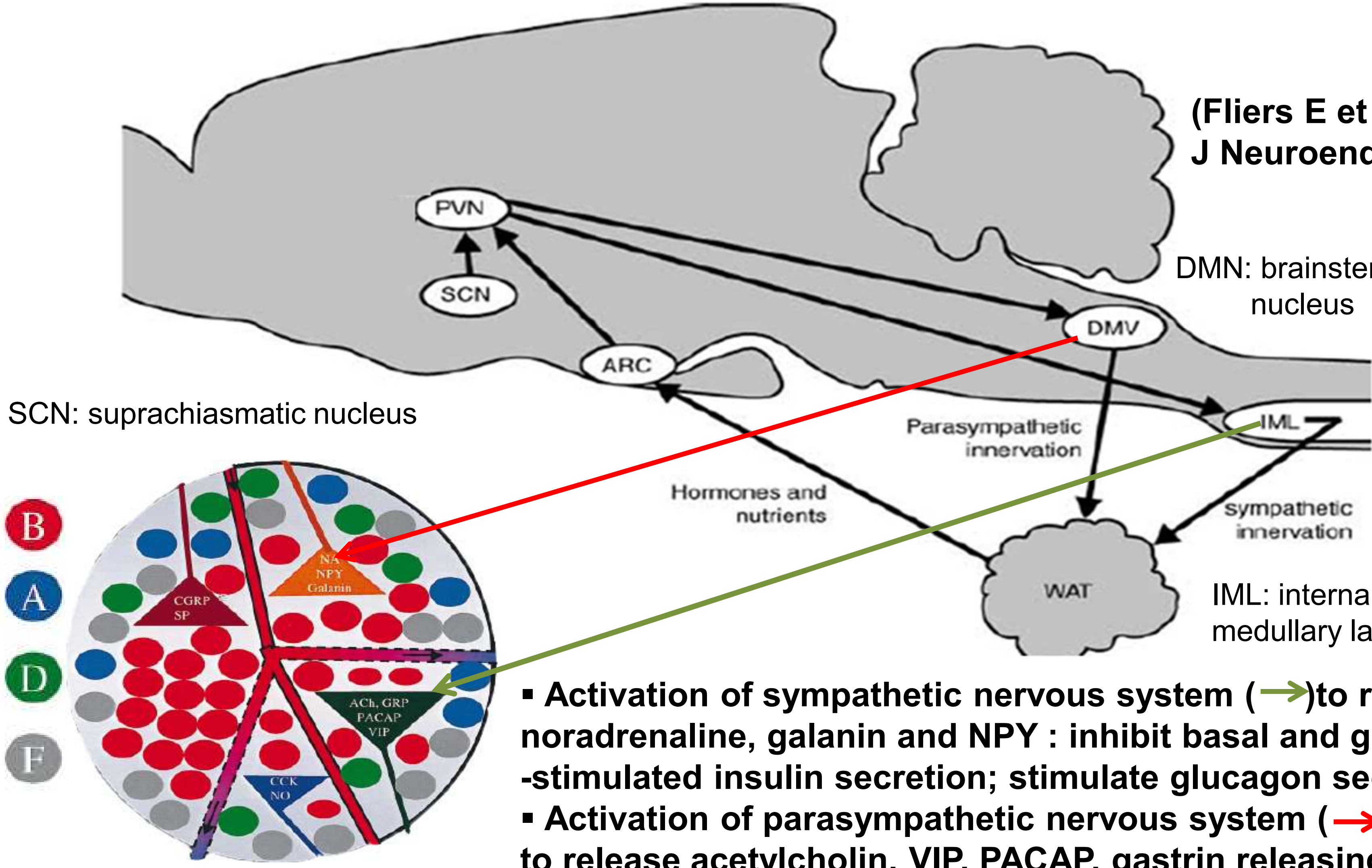
- Functional interaction of adipokines and β-cell function and β-cell mass
  - Direct adipokine effects
  - **Indirect adipokine effects through autonomous nervous system**

The adipoinsular axis to control energy and glucose homeostasis



Kieffer TJ & Hanener JF. Am J Physol Endocrin Metab, 2000

Circuit of white adipose tissue and islets into CNS



(Fliers E et al. J Neuroendo, 2003)

DMN: brainstem nucleus

SCN: suprachiasmatic nucleus

IML: internal medullary lamina

- Activation of sympathetic nervous system (→)to release noradrenaline, galanin and NPY : inhibit basal and glucose -stimulated insulin secretion; stimulate glucagon secretion
- Activation of parasympathetic nervous system (→) to release acetylcholin, VIP, PACAP, gastrin releasing hormones (GRP) : stimulate insulin and glucagon secretion

ICV adipokines and β-cell function and mass

- **ICV leptin, resistin, and leptin+resistin**
- **ICV adiponectin**
- **ICV leptin with/without sympathetic nervous system into the pancreas**

Characteristics of 90% pancreatectomized rats

- **90% pancreatectomized rats (partial pancreatectomized rats):**
  - After removing 90% of the pancreas, it regrows up to 40-50% of the intact pancreas within 2 weeks from the surgery.
  - β-cell mass : about 50-60% of the Sham non-diabetic rats since β-cell density of Px rats is greater than Sham rats
  - Insulin secretion : about 50-60% of Sham rats, in parallel with β-cell mass
  - Insulin resistance: gradually exacerbated after removal of the pancreas and a high fat diet accelerates insulin resistance
  - Non-obese

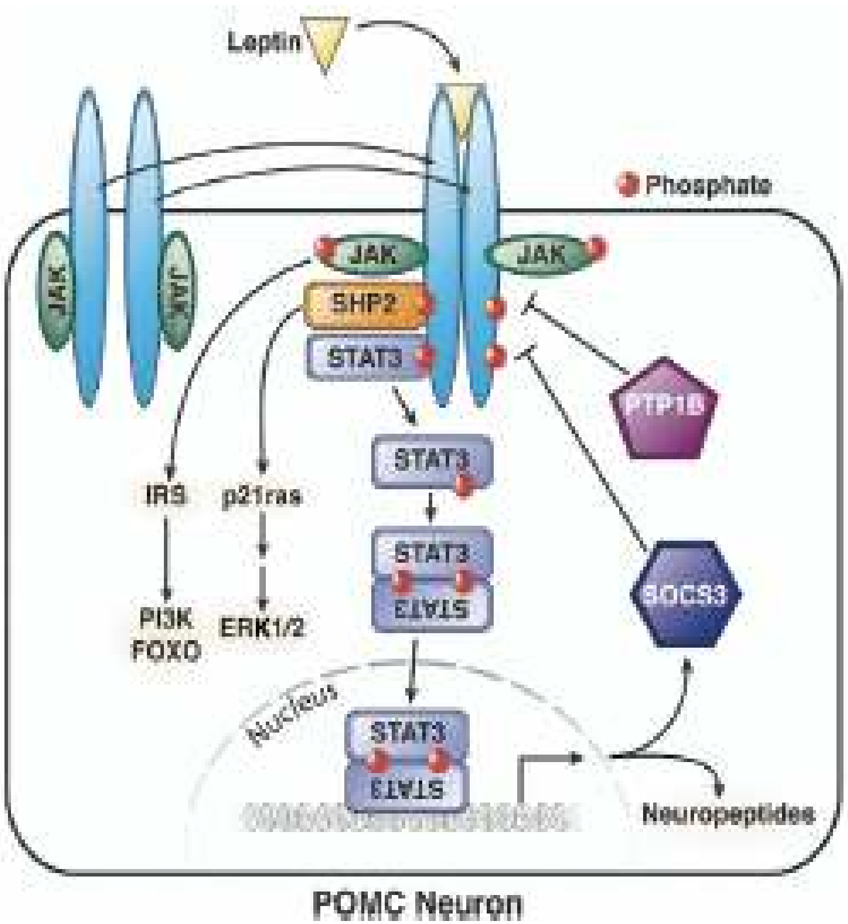
- **Asian type 2 diabetes:**
  - Non-obese
  - No hyperinsulinemia- usually have normoinsulinemia or hypoinsulinemia
  - Increased insulin resistance

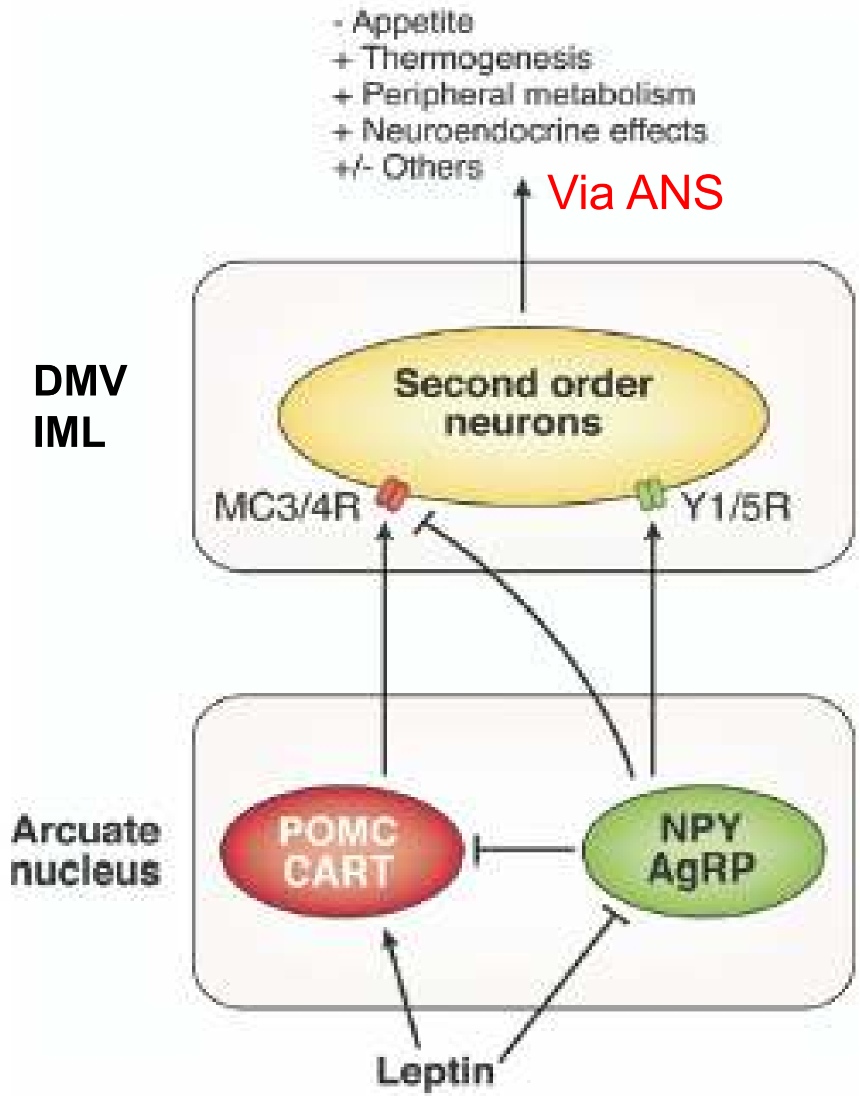
→ **90% pancreatectomzed rat is a good animal model for Asian type 2 diabetes.**

ICV leptin and resistin effect on glucose metabolism

Park S et al. Endocrinology, 2008

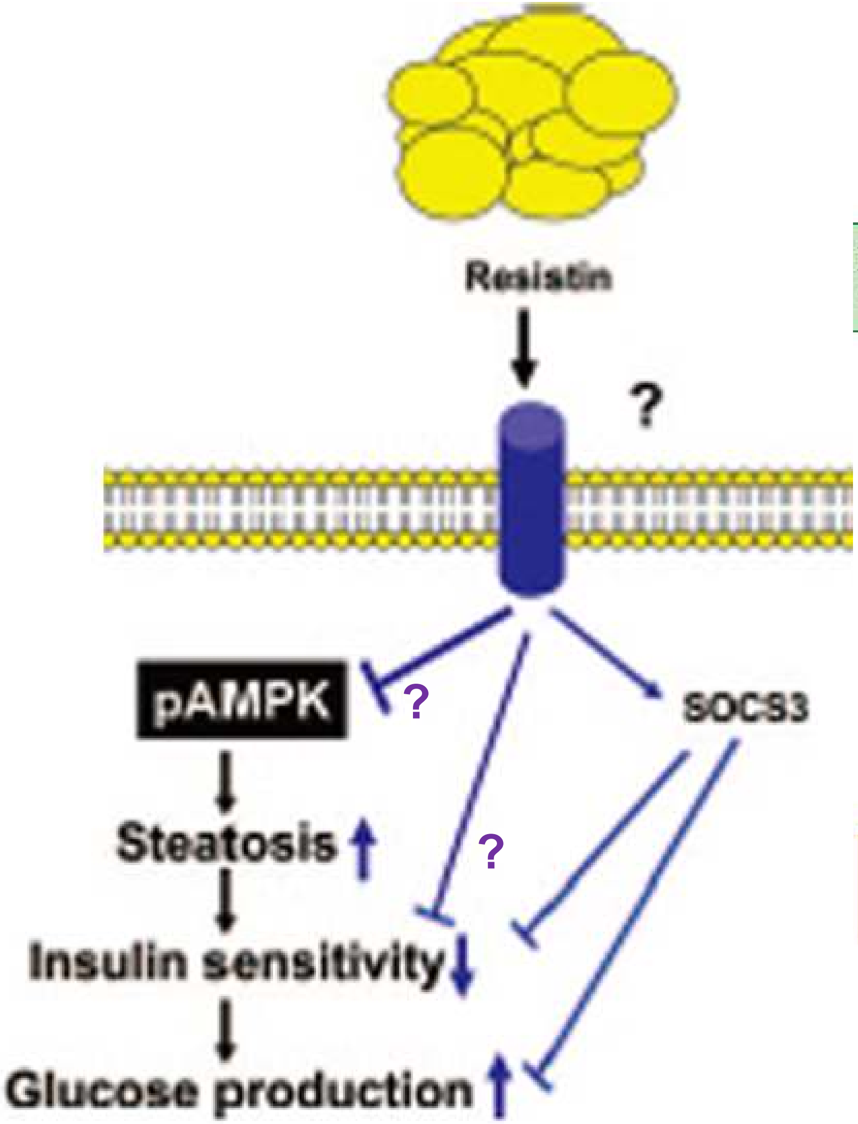
Potential action of leptin on hypothalamus

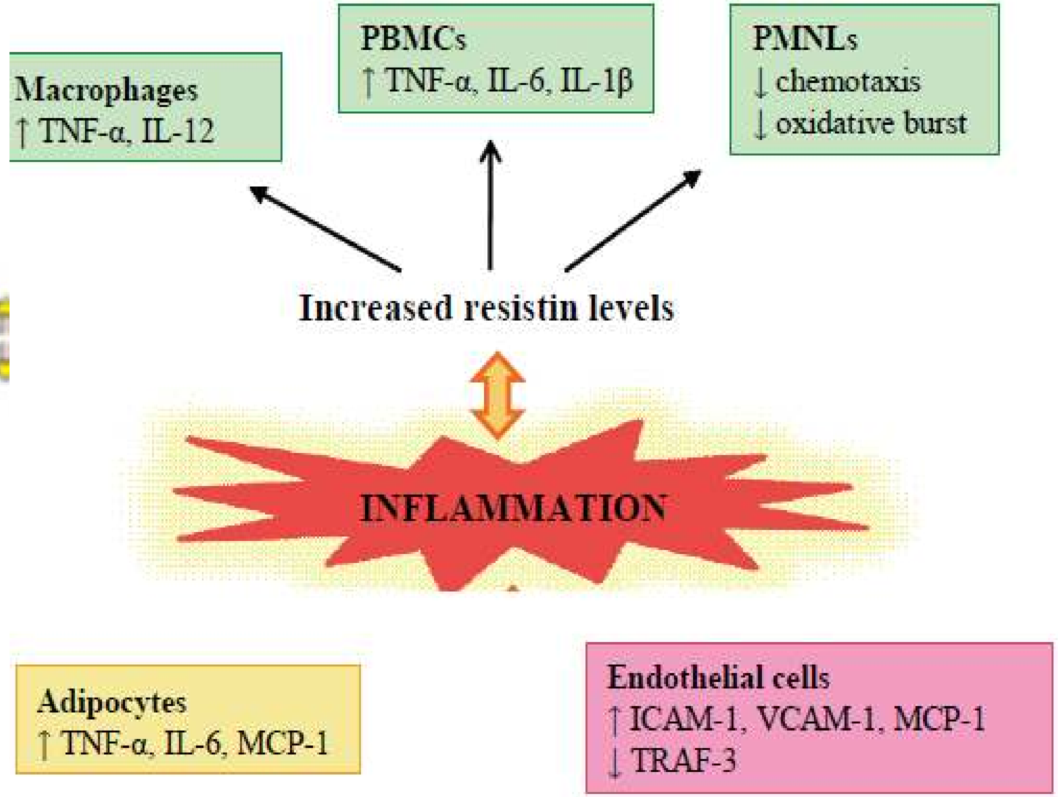




Badman MK & Flier JS. Gastroenterology, 2007

Action mechanism of resistin

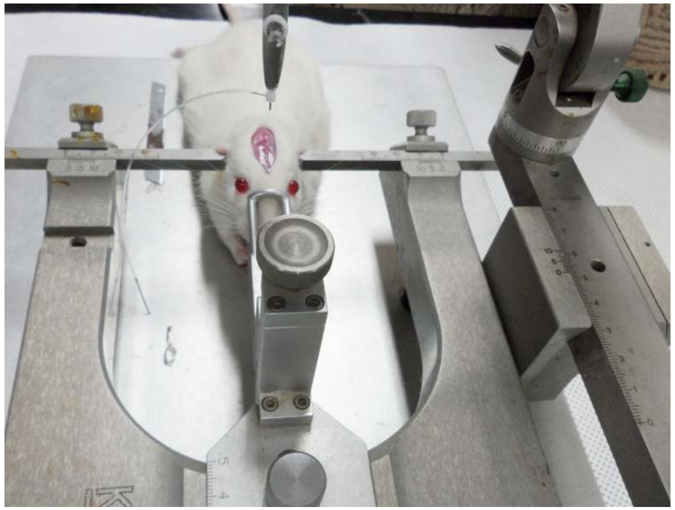




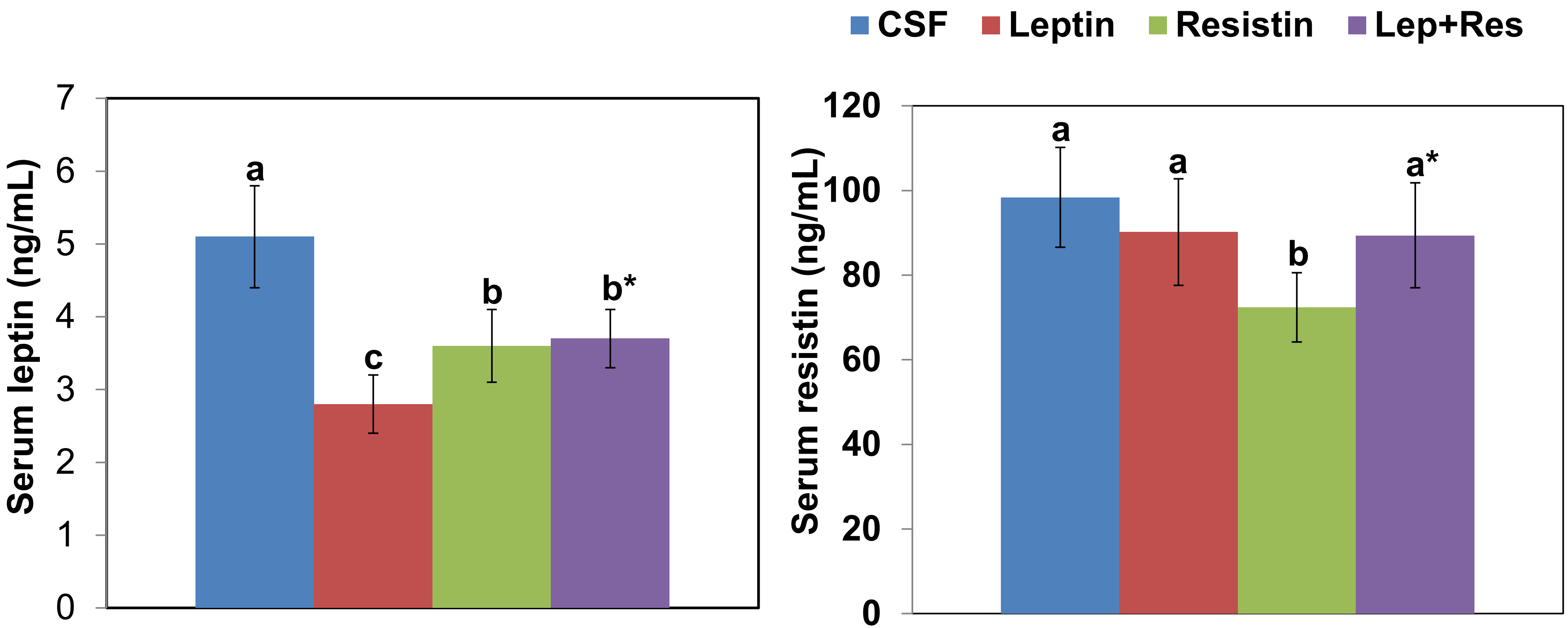
(Stofkova A. Endocrine Regul, 2010)

Experimental design

0	1	2	5	6 weeks
Purchase 219±12g Male rats	Px	ICV Leptin, resistin leptin+resistin, CSF infusion via osmotic pump (80 ng/day leptin clamp 2 ug/day resistin)	Catheter insertion	Hyperglycemic clamp BrdU injection



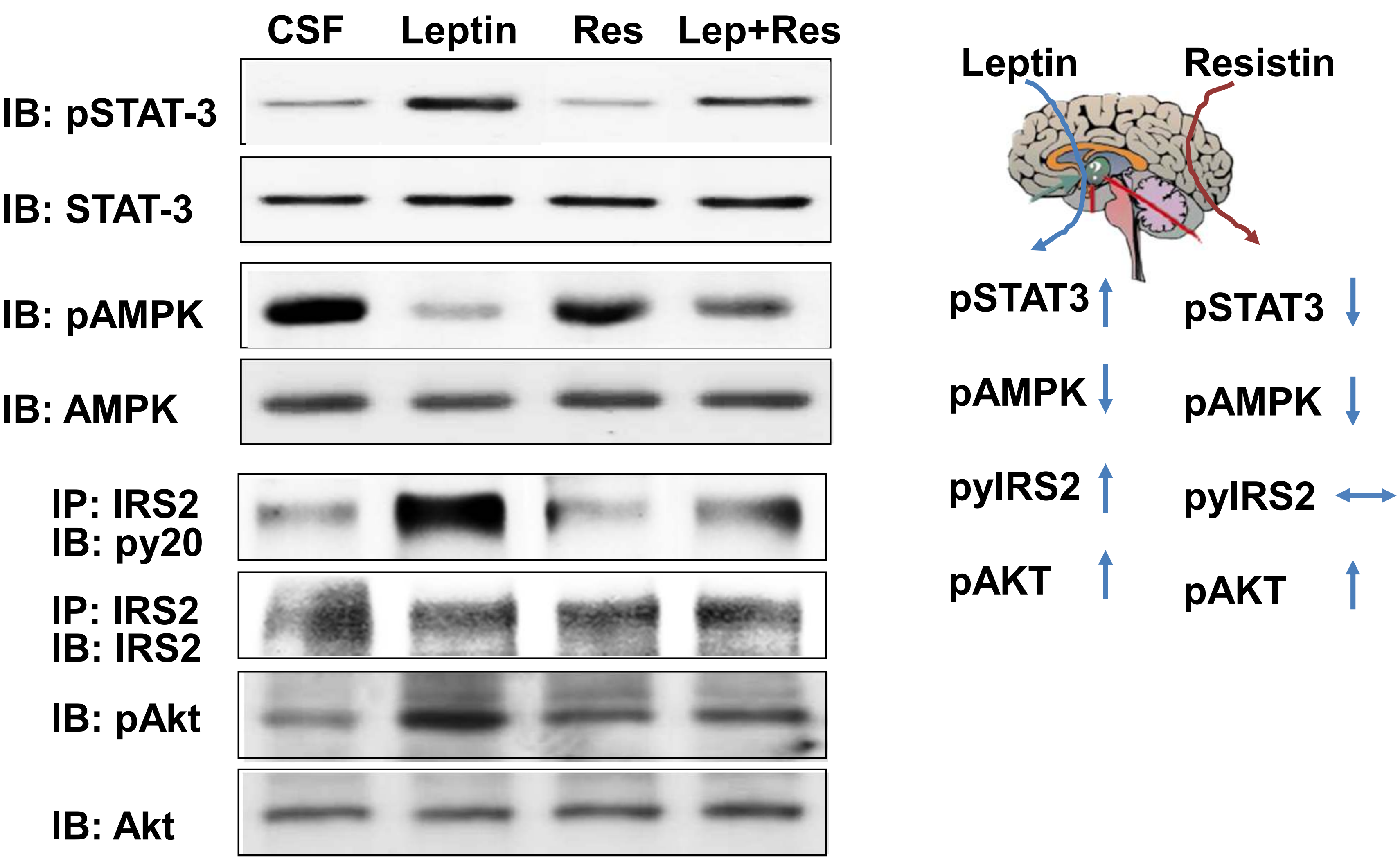
Serum leptin and resistin levels



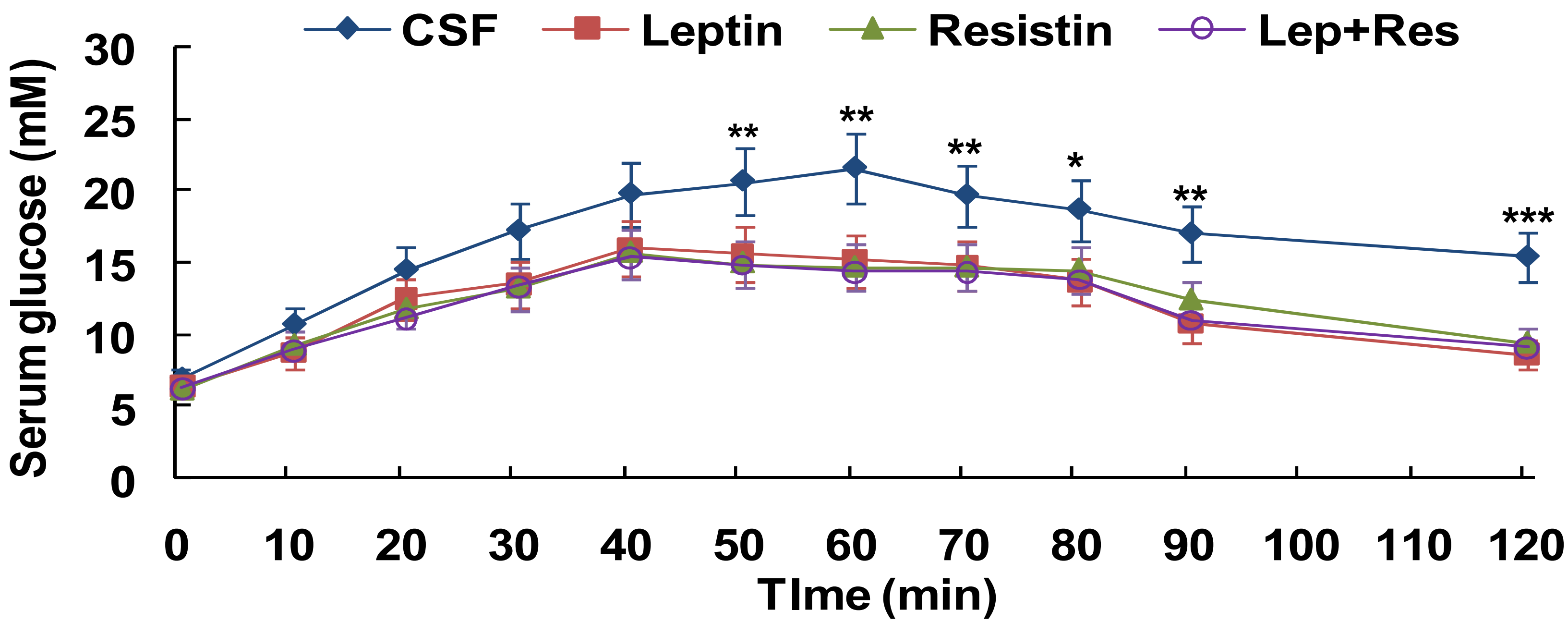
*Significantly different among the groups at $p<0.05$.

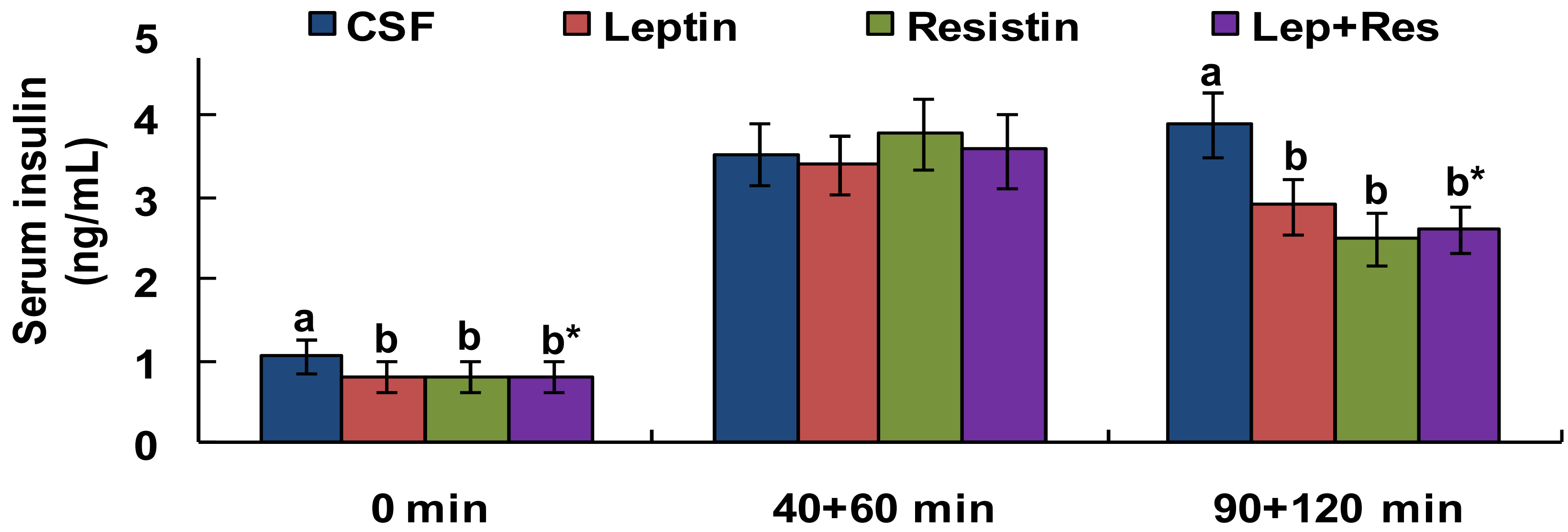
[a,b,c]Means of the bars with different superscripts were significantly different

Leptin and insulin signaling in the hypothalamus

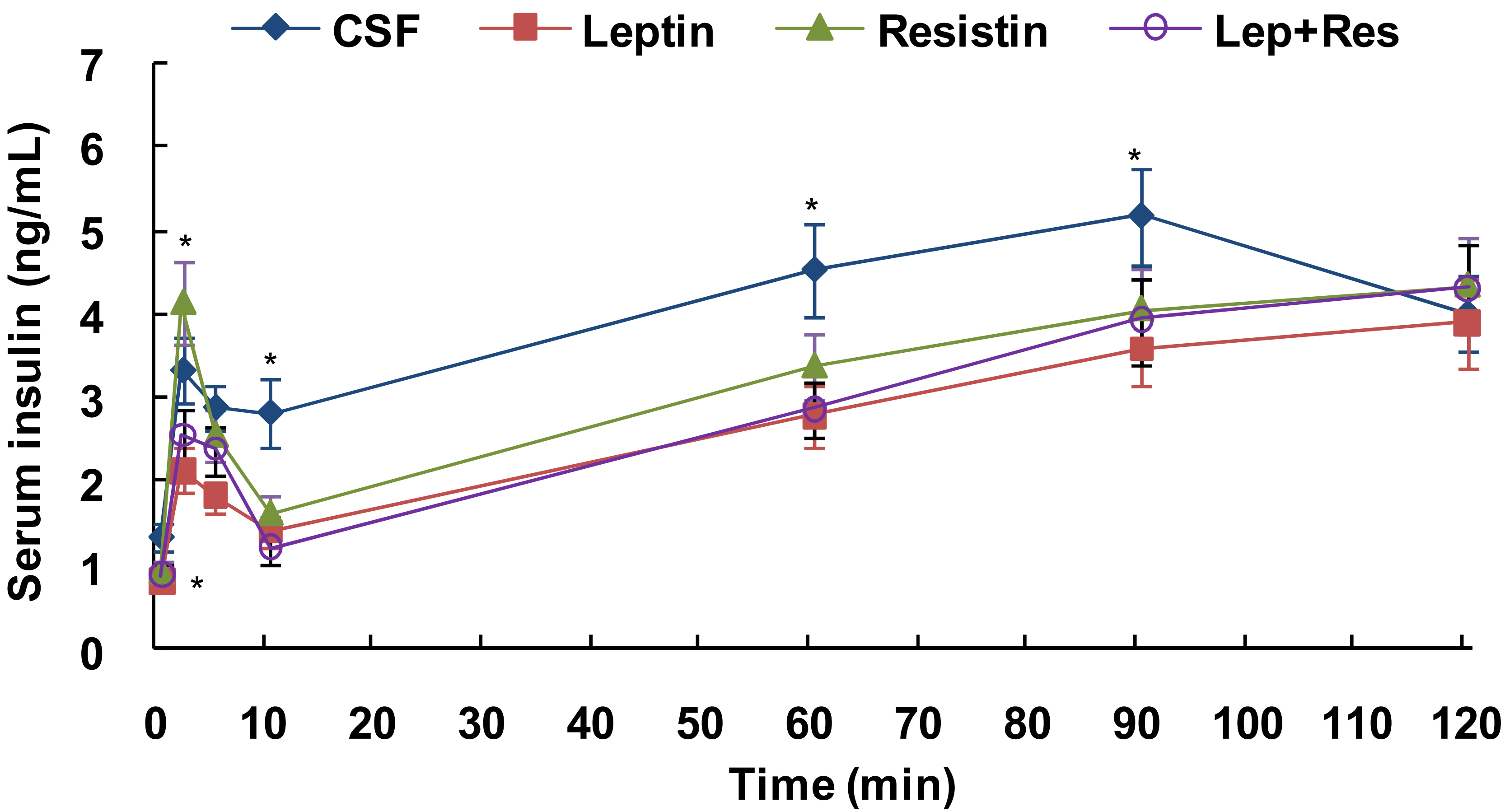


Glucose tolerance



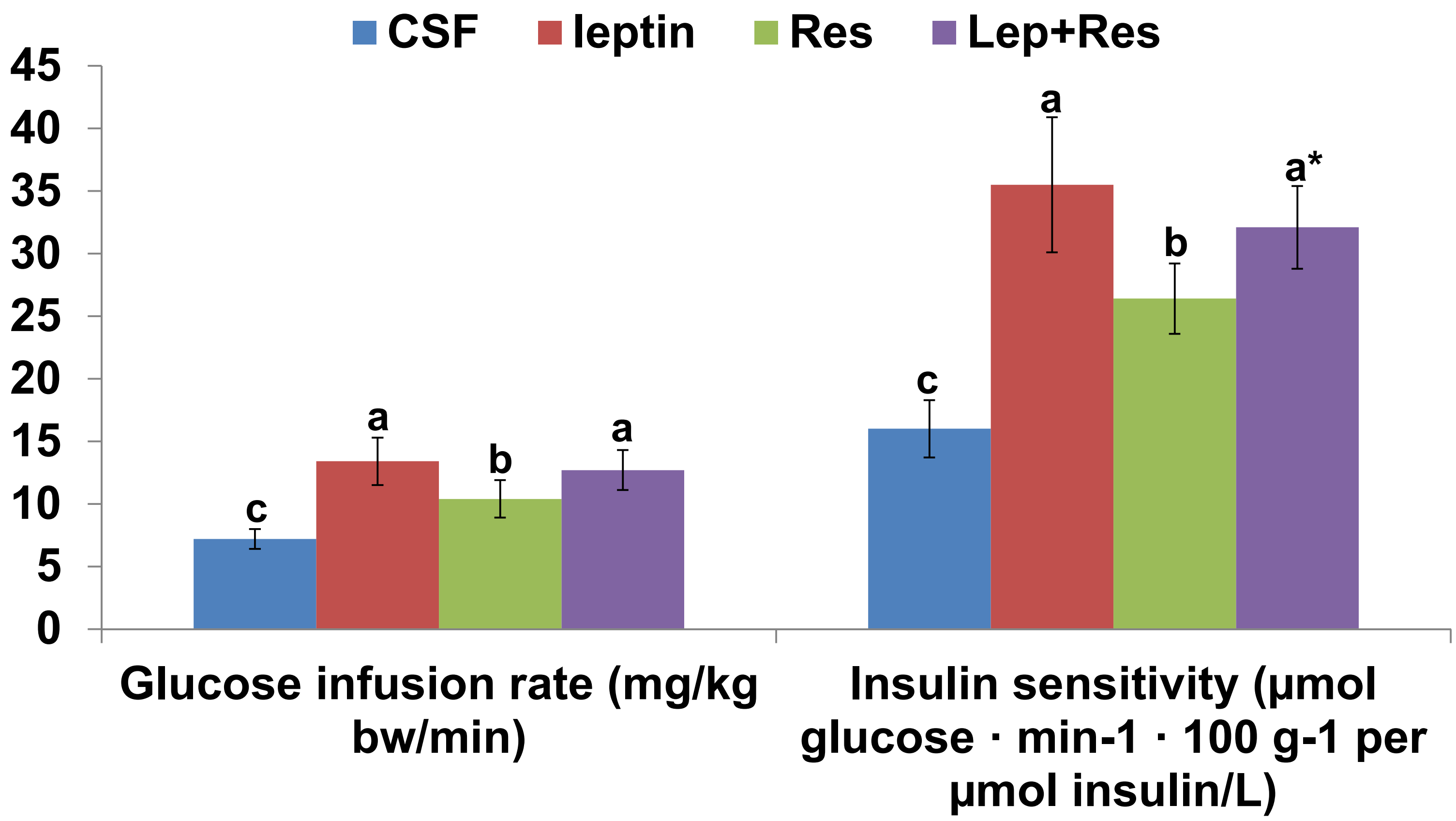


Insulin secretion during hyperglycemic clamp



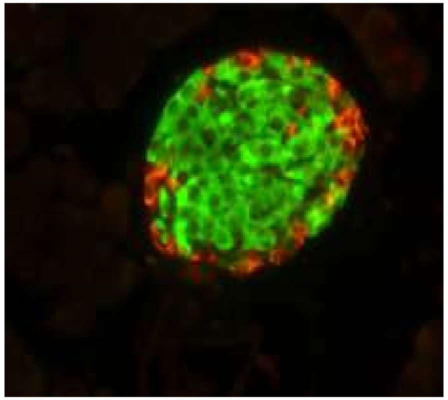
*Significantly different among the groups at p<0.05.

Insulin sensitivity at hyperglycemic state

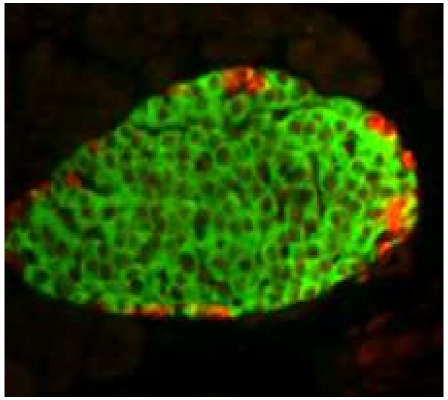


[a,b,c]Means of the bars with different superscripts were significantly different

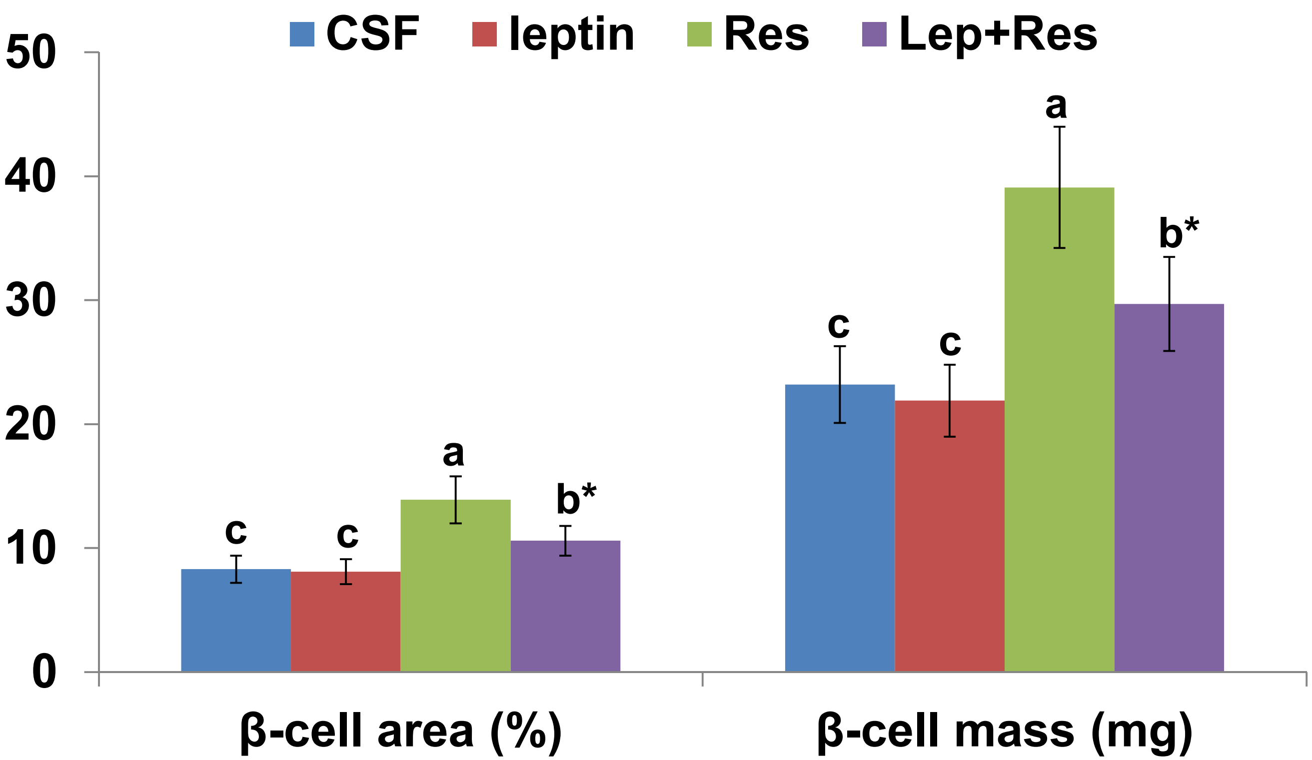
β-cell area and mass



CSF

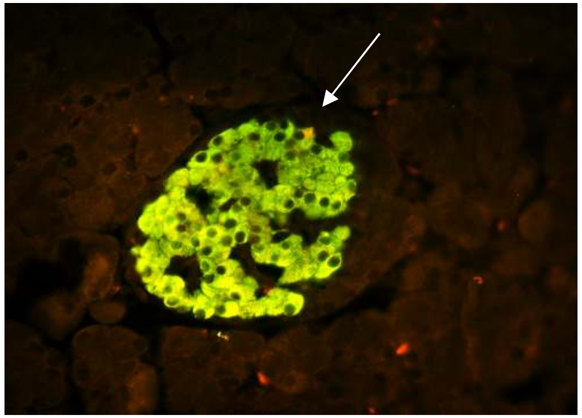


Resistin

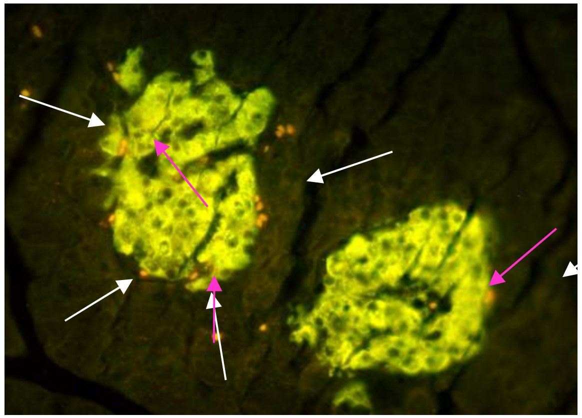


[a,b,c]Means of the bars with different superscripts were significantly different

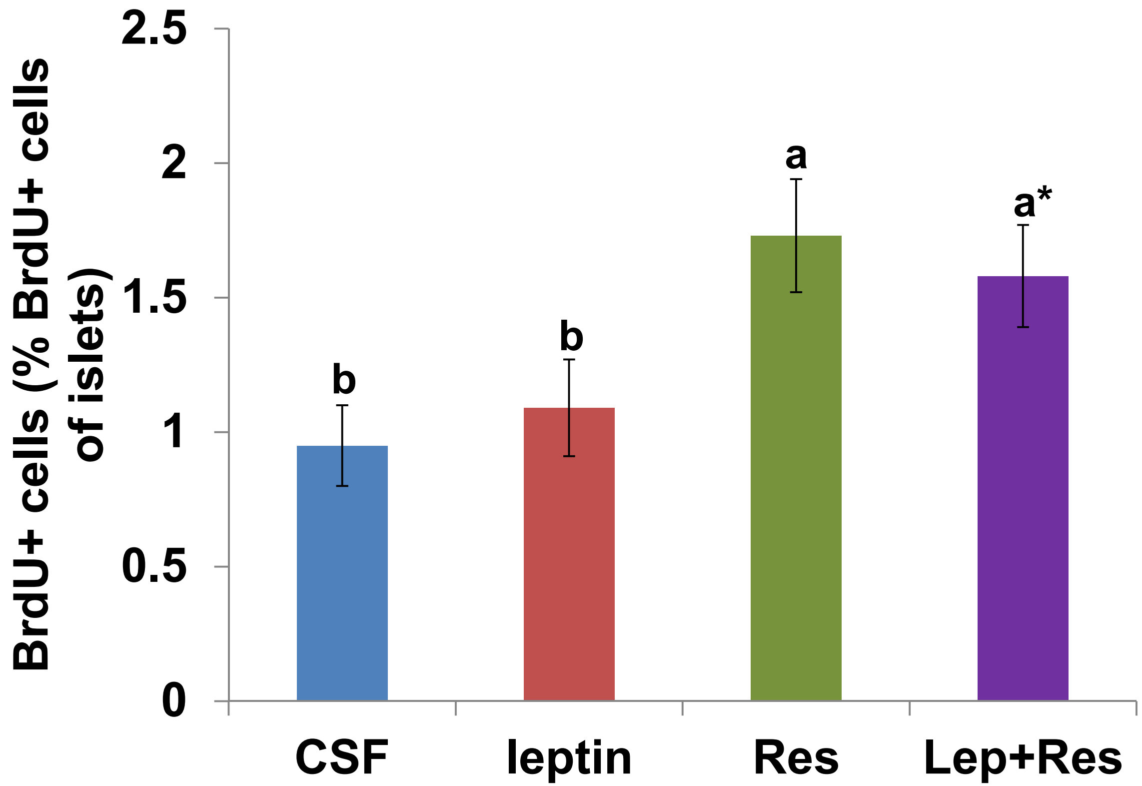
β-cell proliferation



Cont

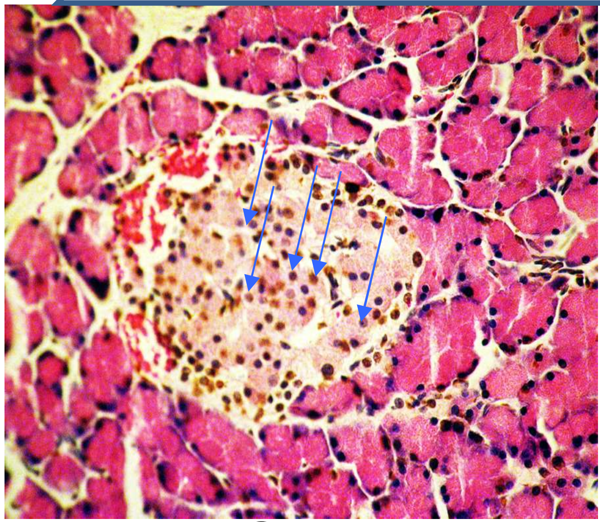


Resistin



[a,b,c]Means of the bars with different superscripts were significantly different

β-cell apoptosis



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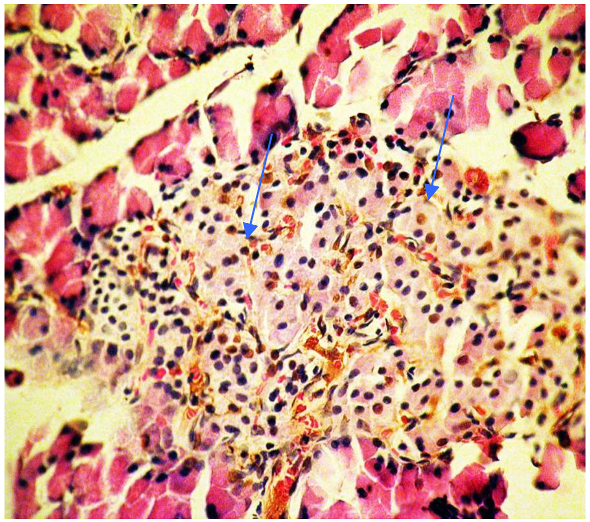
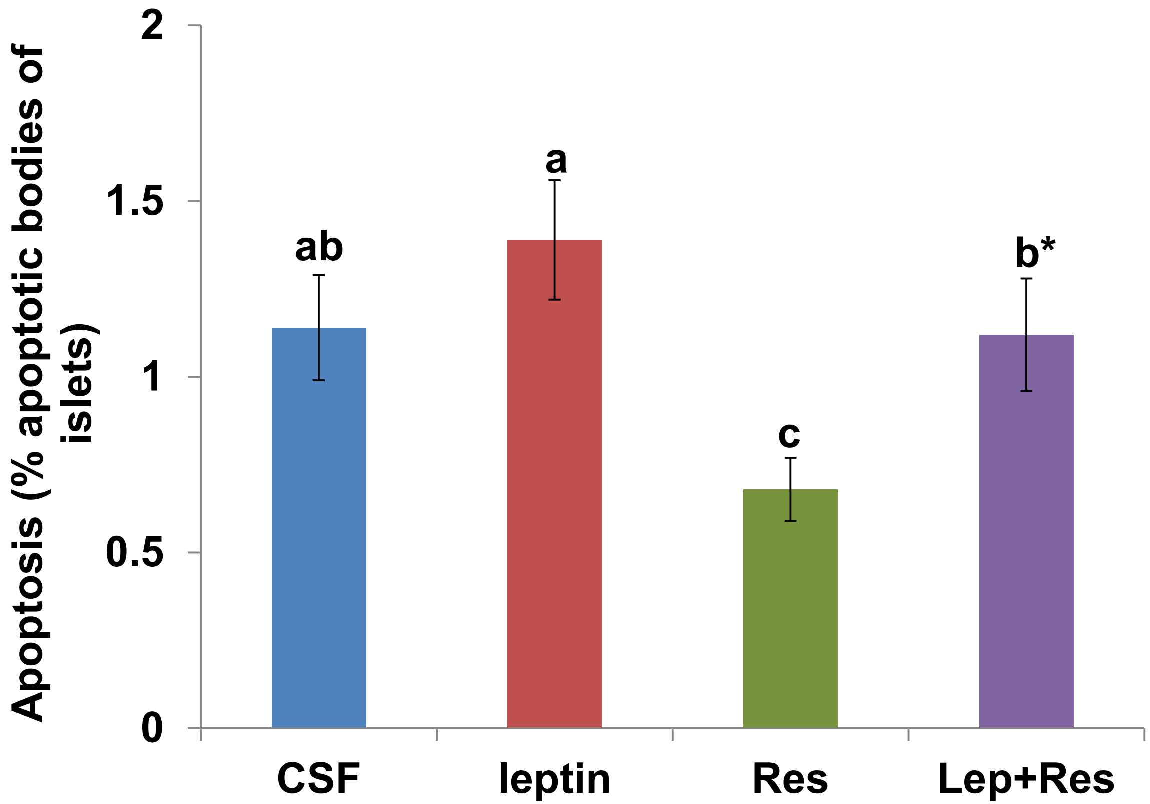


Resistin



[a,b,c]Means of the bars with different superscripts were significantly different

Summary

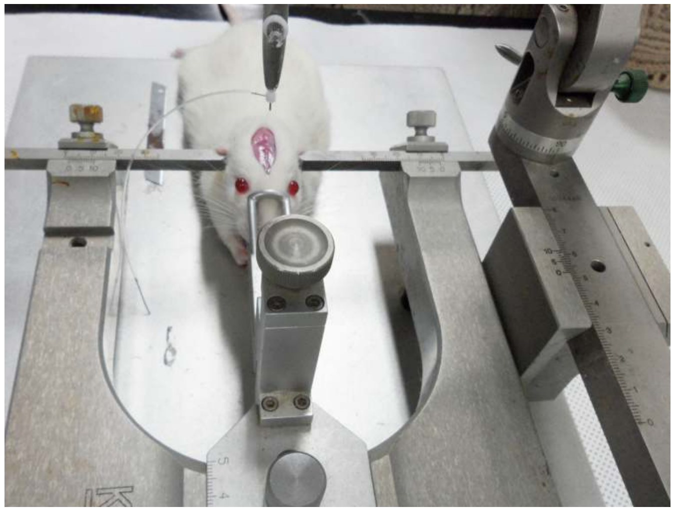
- Both central leptin and resistin improved glucose tolerance.
  - ICV leptin inhibited insulin secretion but potentiated insulin sensitivity at hyperglycemic state.
  - ICV resistin improved first phase insulin secretion and increased β-cell mass.
  - The combination of ICV leptin+resistin have additive and complementary effects.

ICV leptin effect on glucose metabolism through sympathetic nervous system

Park S et al. Life Sci, 2010

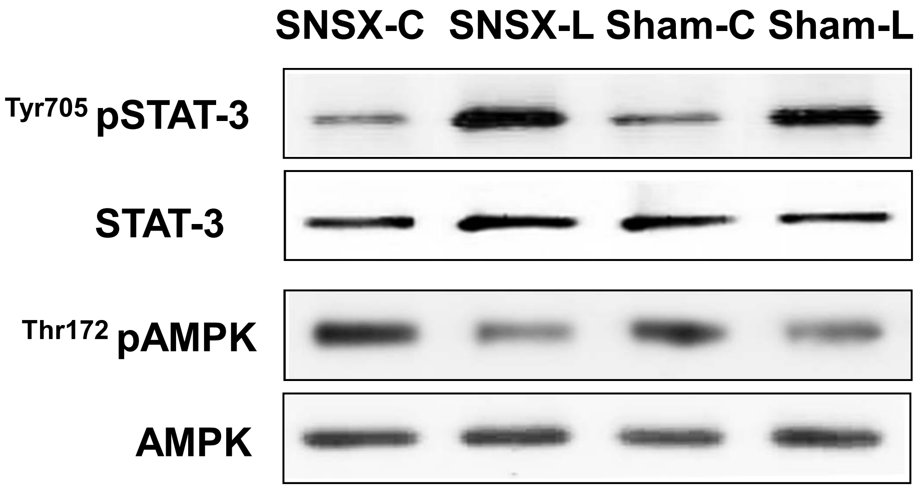
Long-term ICV leptin on glucose metabolism

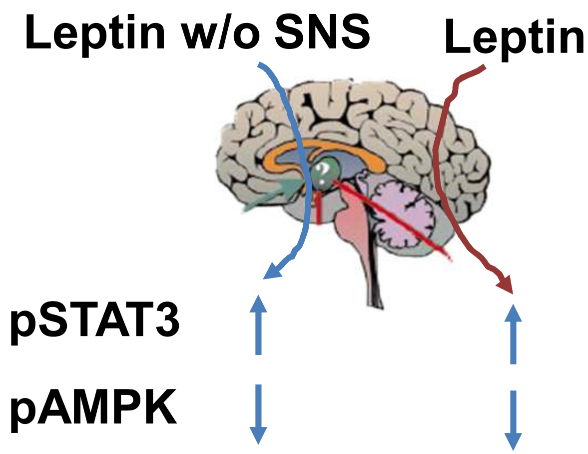
0	1	2	3	6	7 weeks
Purchase 212±18g Male rats	Px	SNS denervation ICV implantation	ICV Leptin CSF injection via osmotic pump (1 ug/day)	Catheter insertion Hyperglycemic clamp	BrdU injection



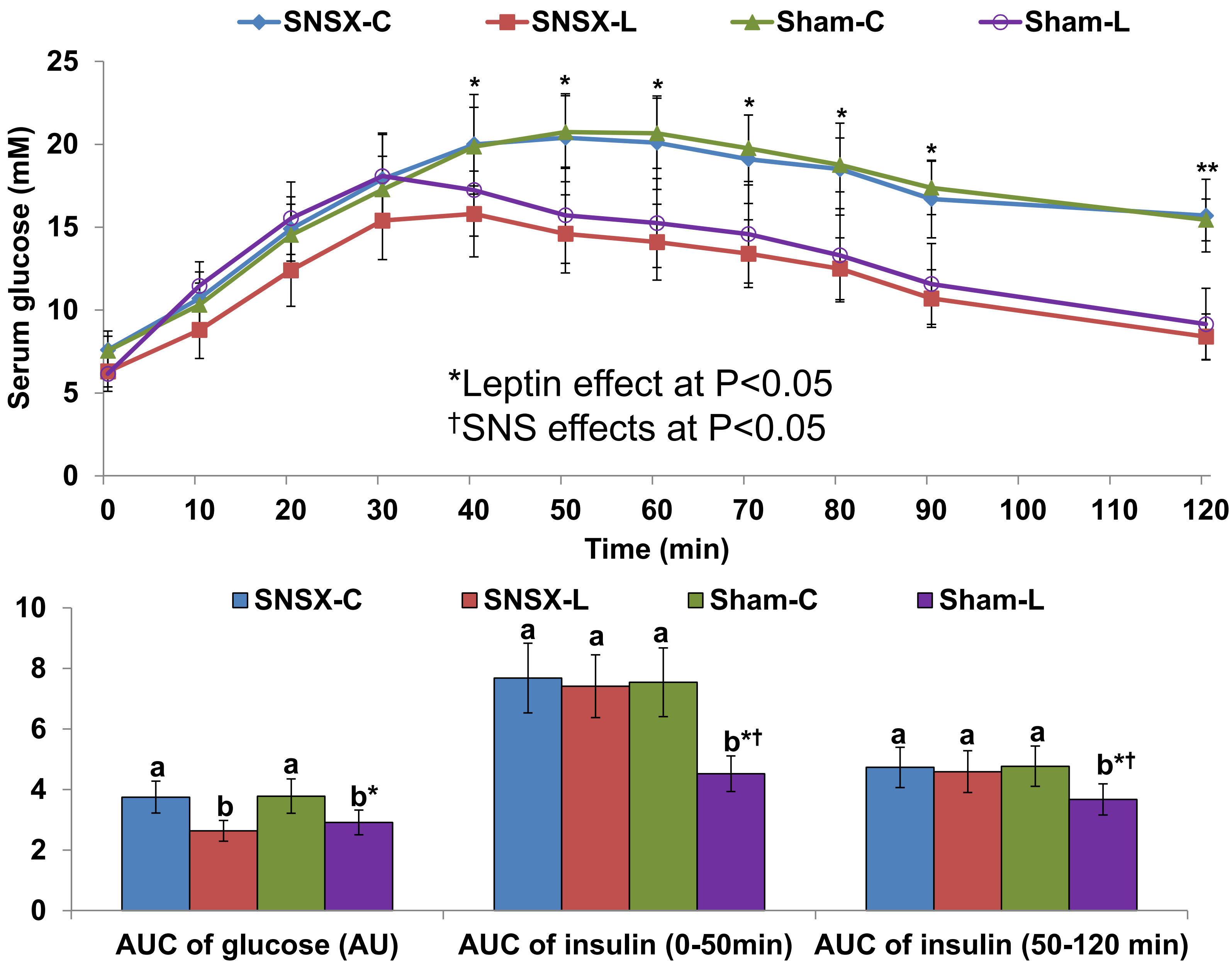
SNS denervation in pancreas (SNSX) :
By chemical (phenol) application in the descending aorta between kidney and pancreas.

Leptin signaling in the hypothalamus

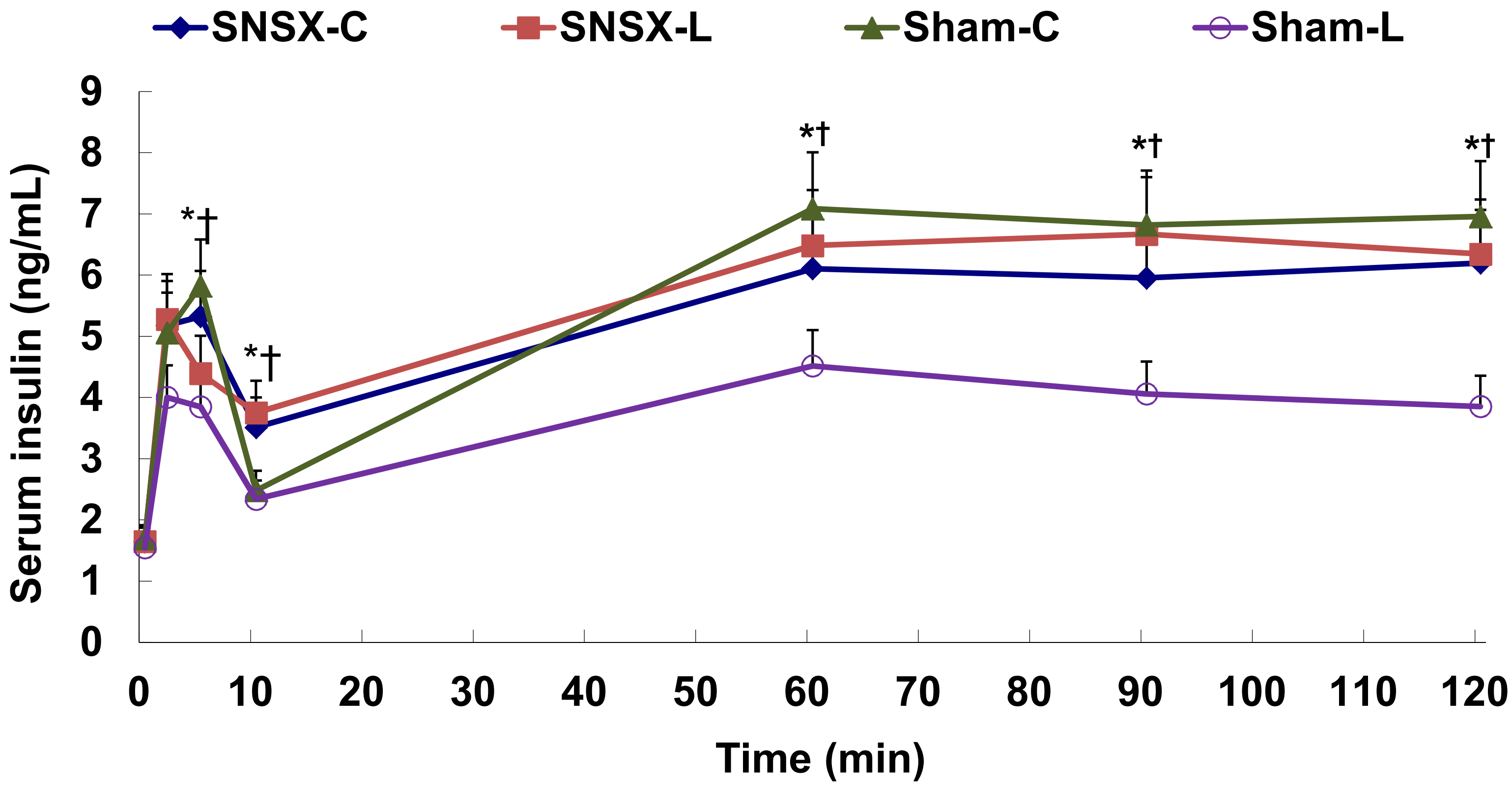




Glucose tolerance



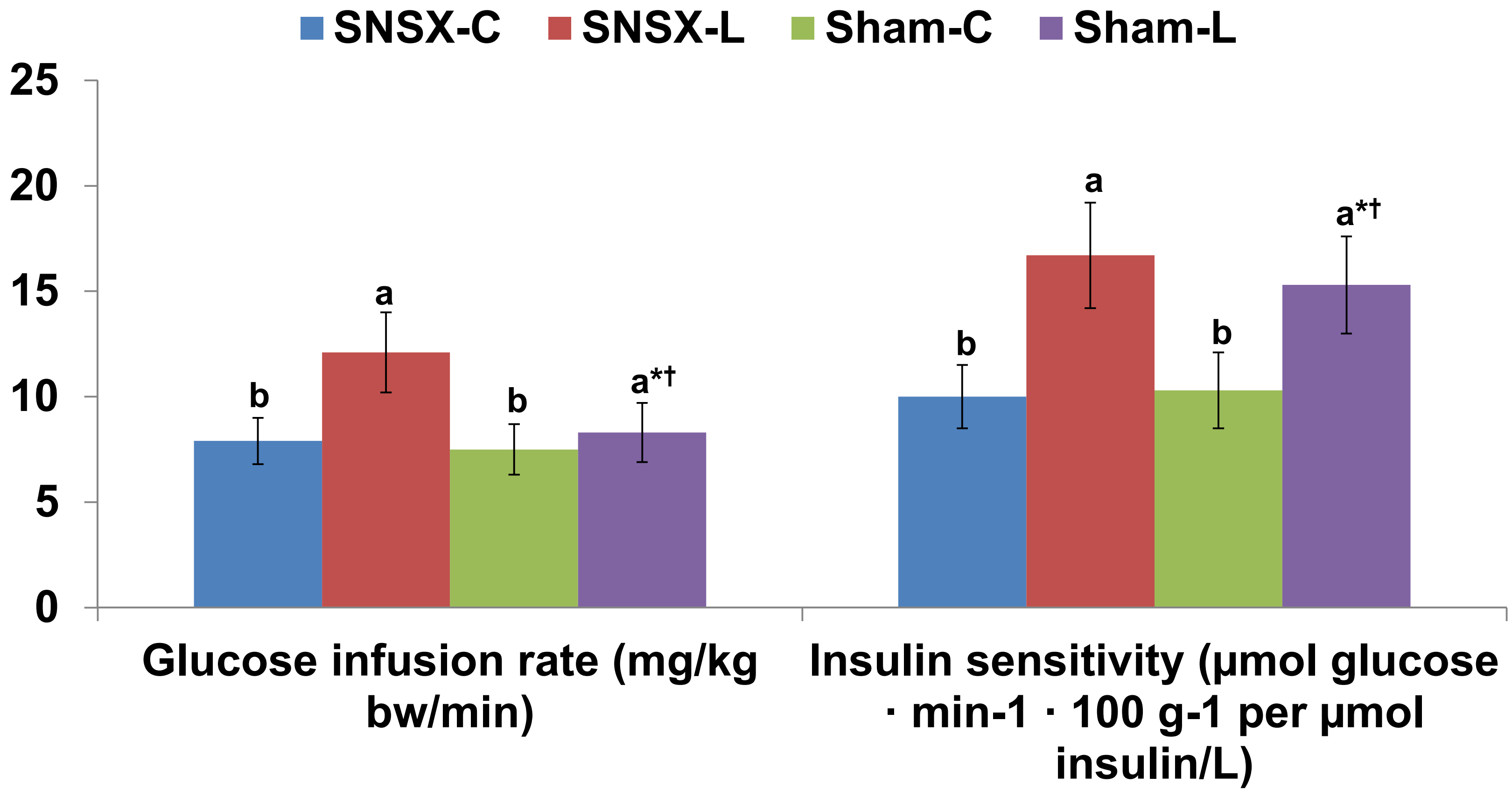
Insulin secretion during hyperglycemic clamp



*Significant effect of leptin at $p<0.05$.

†Significant effect of denervation of sympathetic nervous system into the pancreas (SNSX) at $p<0.05$.

Insulin sensitivity at hyperglycemic state



*Significant effect of leptin at $p<0.05$.
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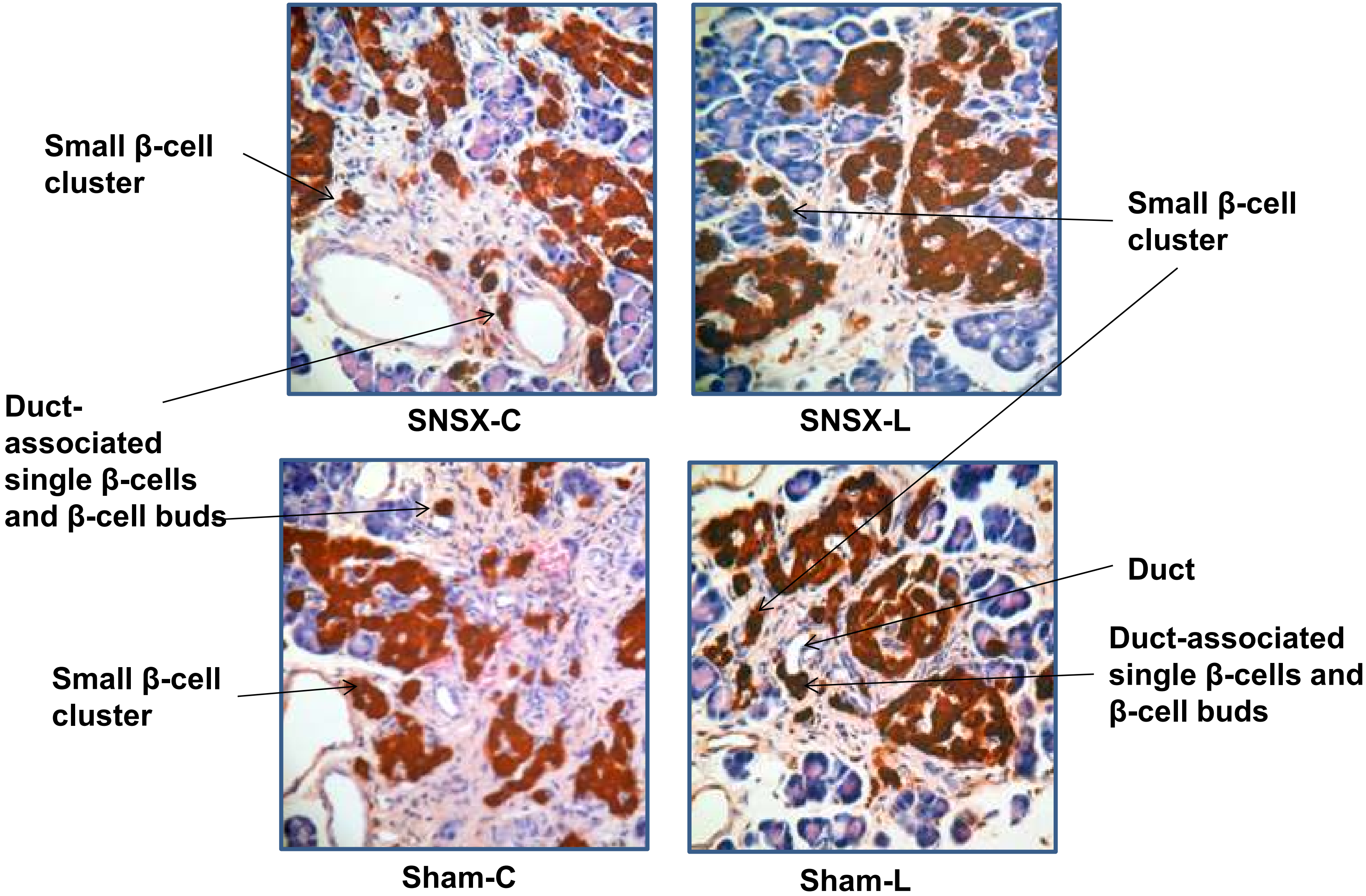
β-cells in the pancreas



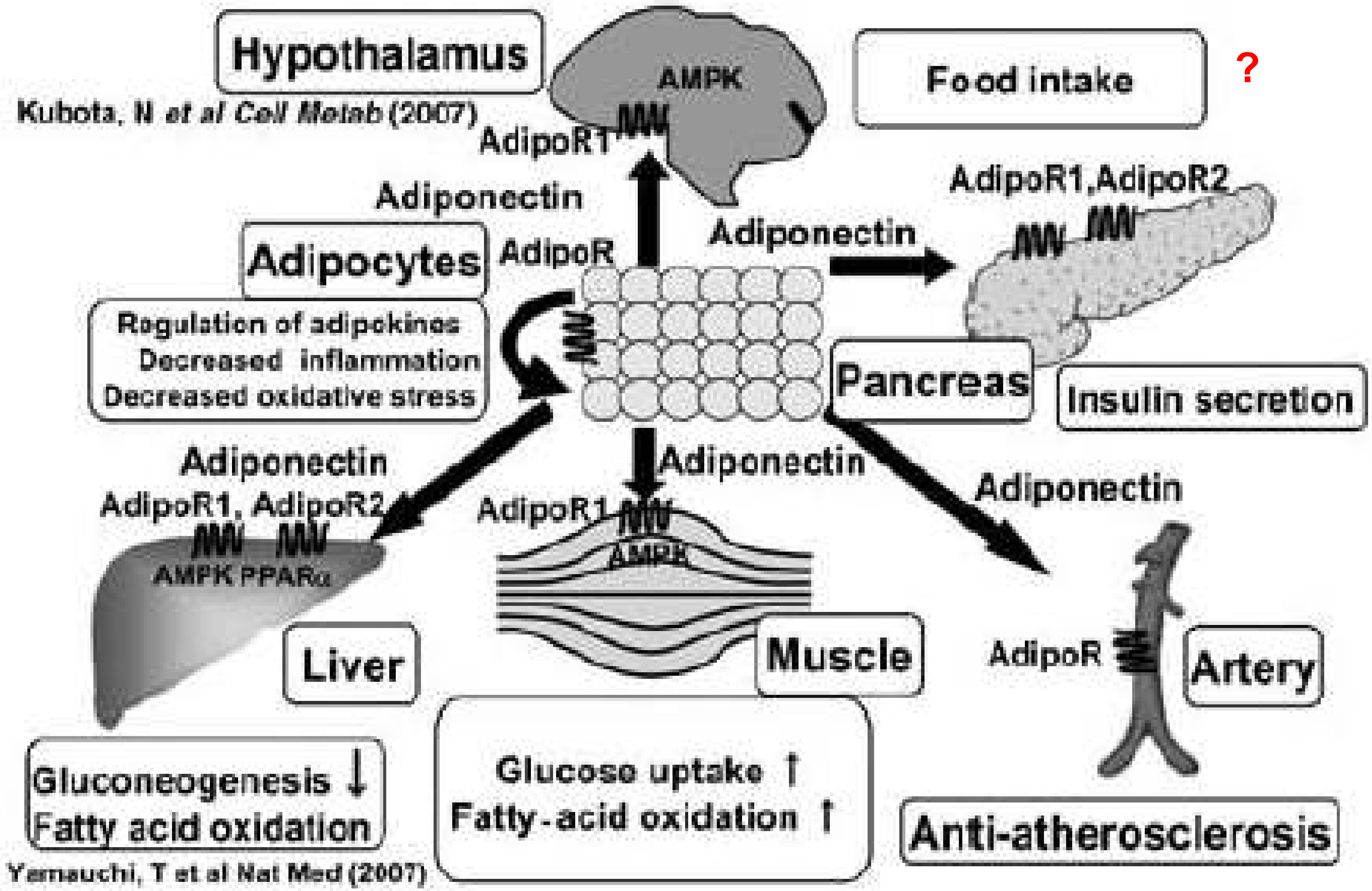
Summary

- Central leptin inhibited insulin β-cell function through sympathetic nervous system.
- However, β-cell mass was not modulated by central leptin.
- Denervation of sympathetic nervous system into the pancreas did not affect insulin sensitivity at hyperglycemic state.

ICV adiponectin effect on glucose metabolism

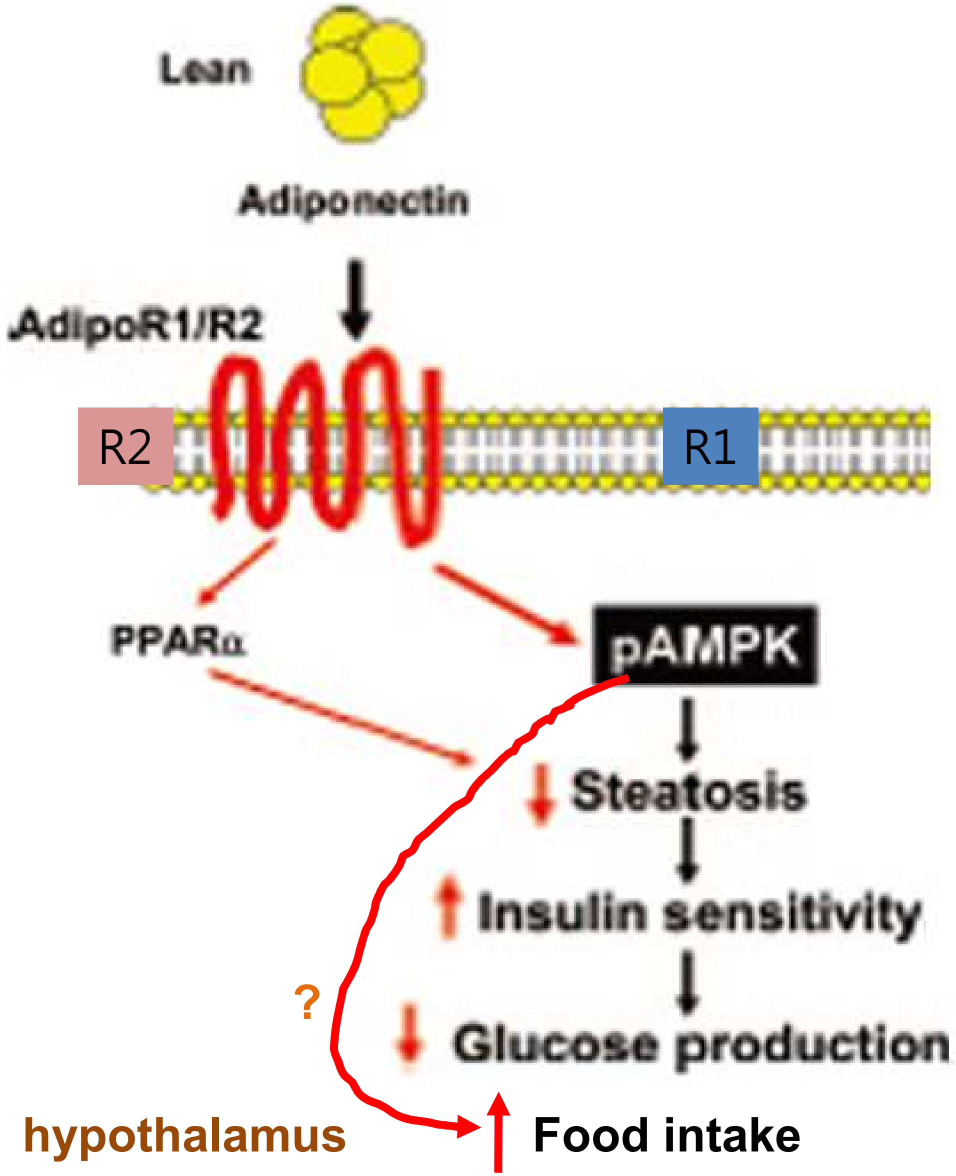
Park S. et al. J Neuroendocrinology 2011

Adiponectin action mechanism



Yamauchi T & Kadowaki T. Int J Obesity 2008

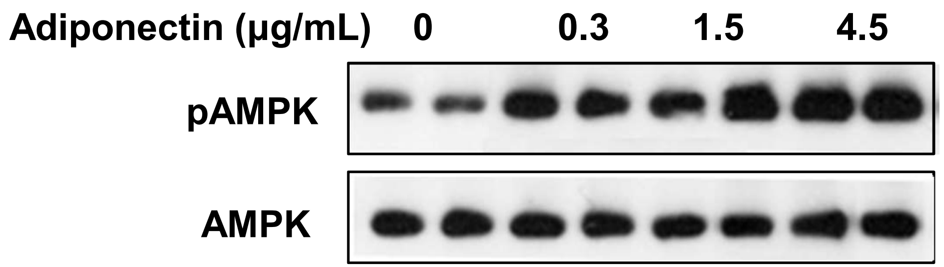
Adiponectin and obesity



(Ahima & Lazar. Mol Endocrin, 2008)

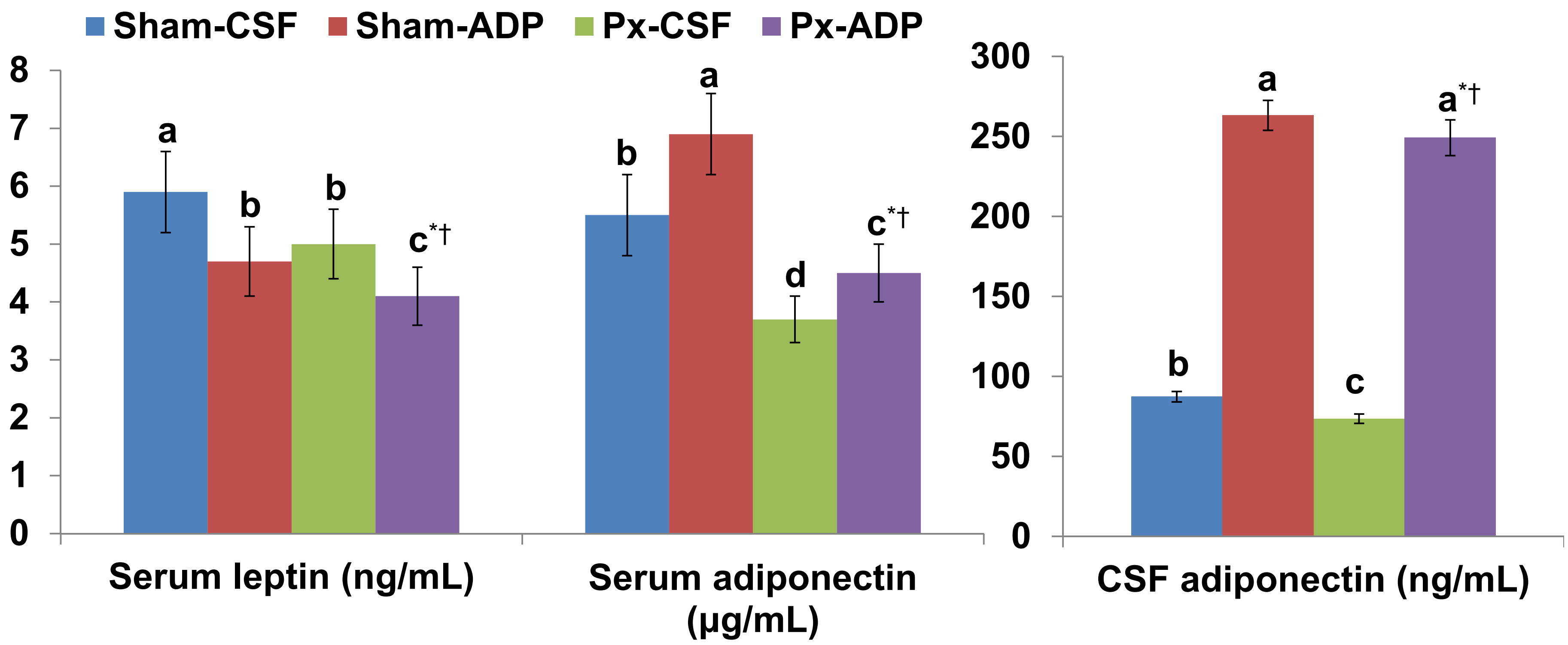
Adiponectin effect on AMPK

In L6 myotubes
For 30 min treatment
of adiponectin



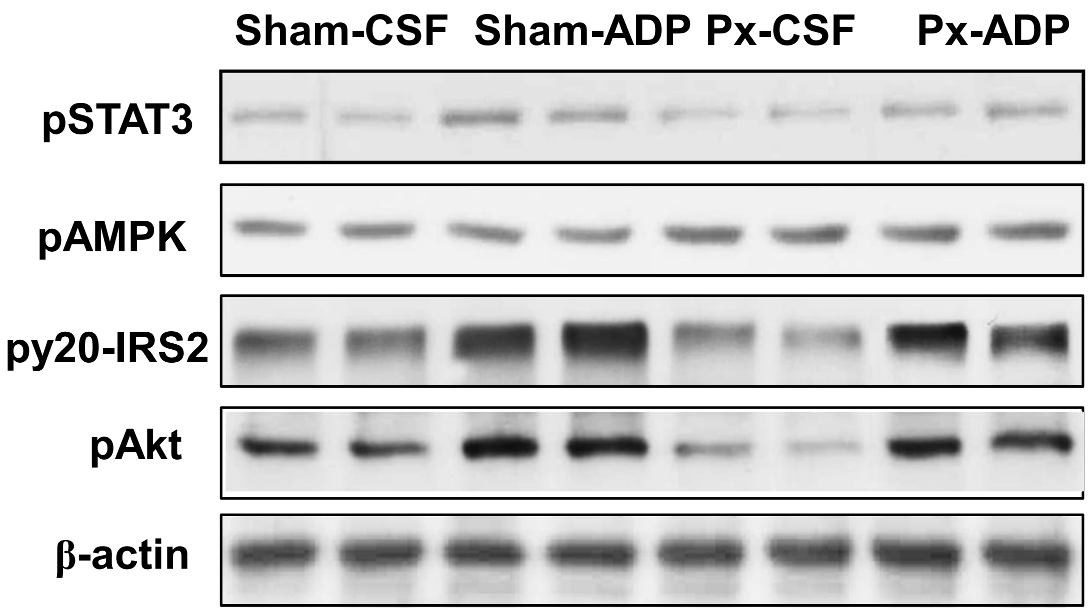
0	1	2	5	6 weeks
Purchase 221±14g Male rats	Px	ICV adiponectin infusion via osmotic pump (1.2 ug/day)	Catheter insertion	Hyperglycemic clamp BrdU injection

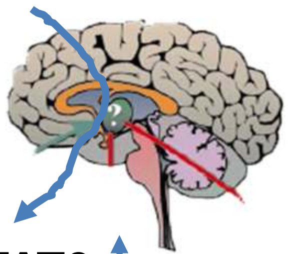
Serum and CSF adiponectin levels



*Significant effect of adiponectin (ADP) at $p<0.05$.
†Significant effect of diabetic status at $p<0.05$.

Leptin and insulin signaling in the hypothalamus





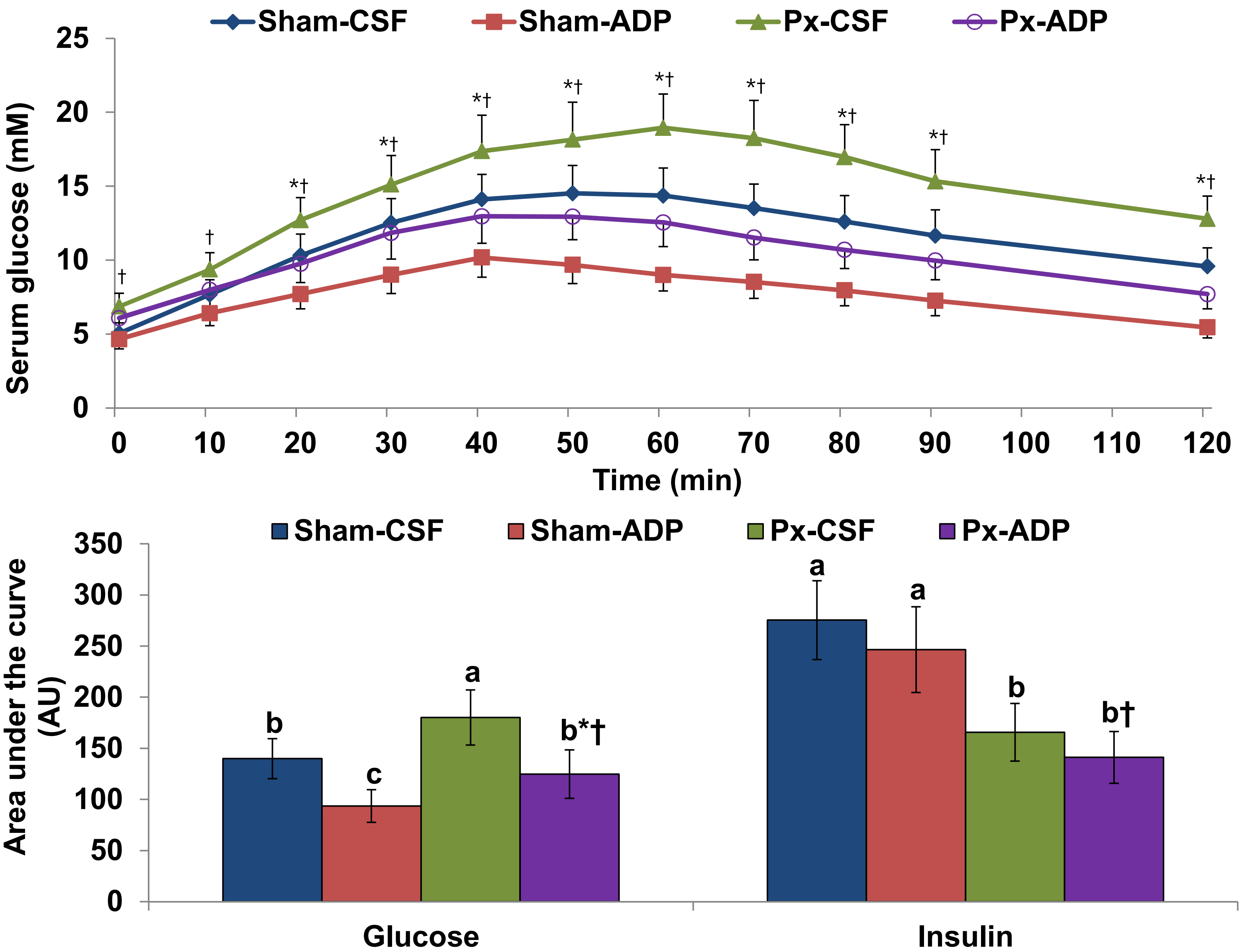
pSTAT3 ↑

pAMPK ↔

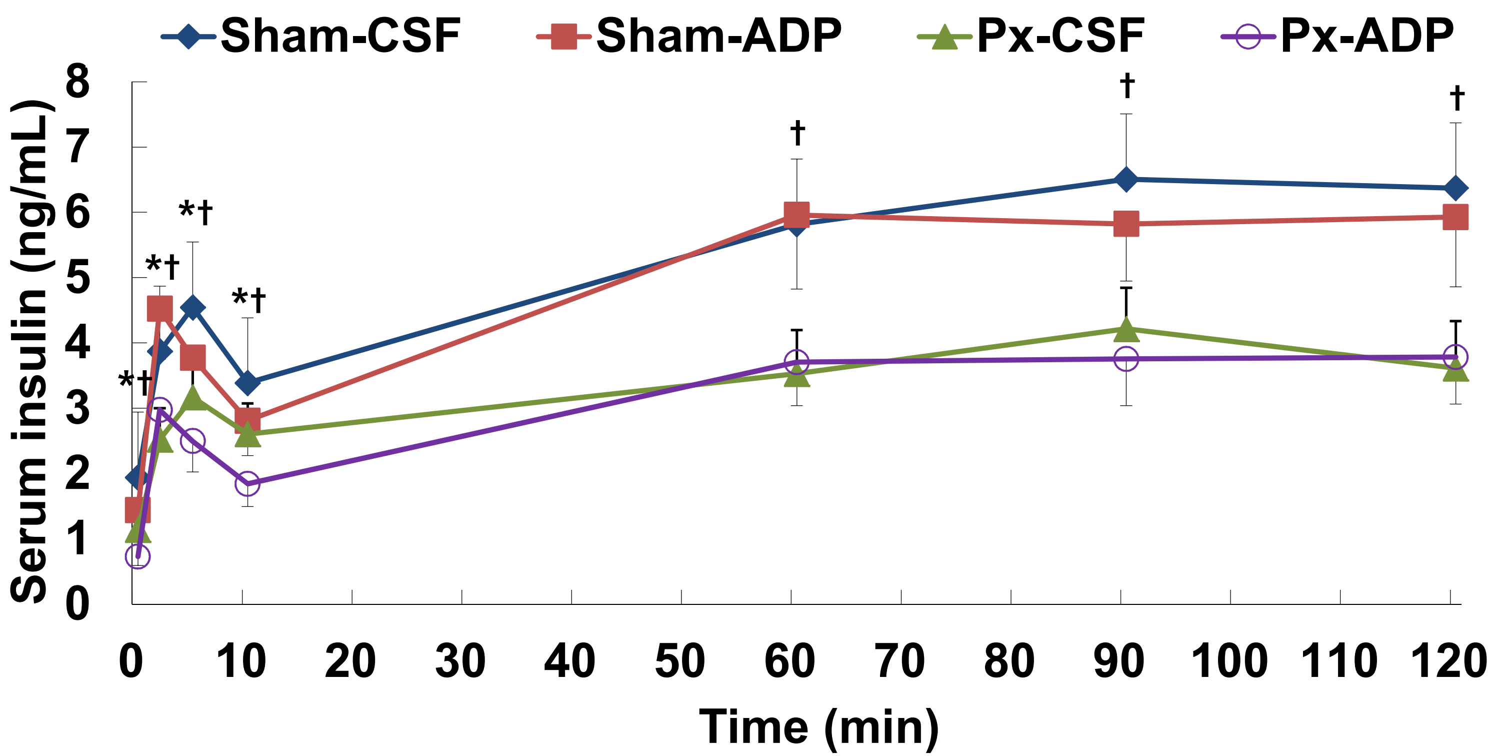
pyIRS2 ↑

pAKT ↑

Glucose tolerance



Insulin secretion during hyperglycemic clamp



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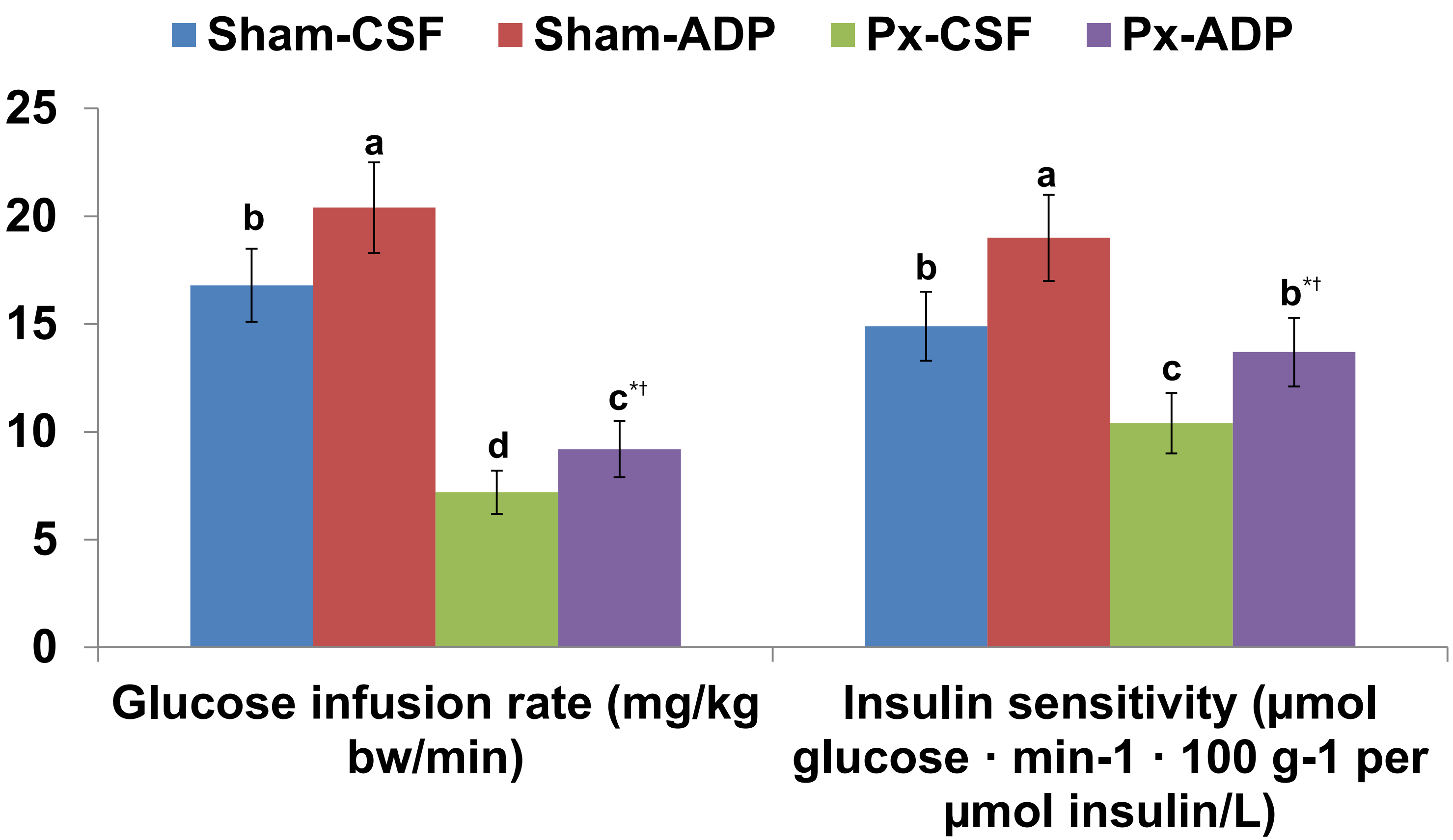
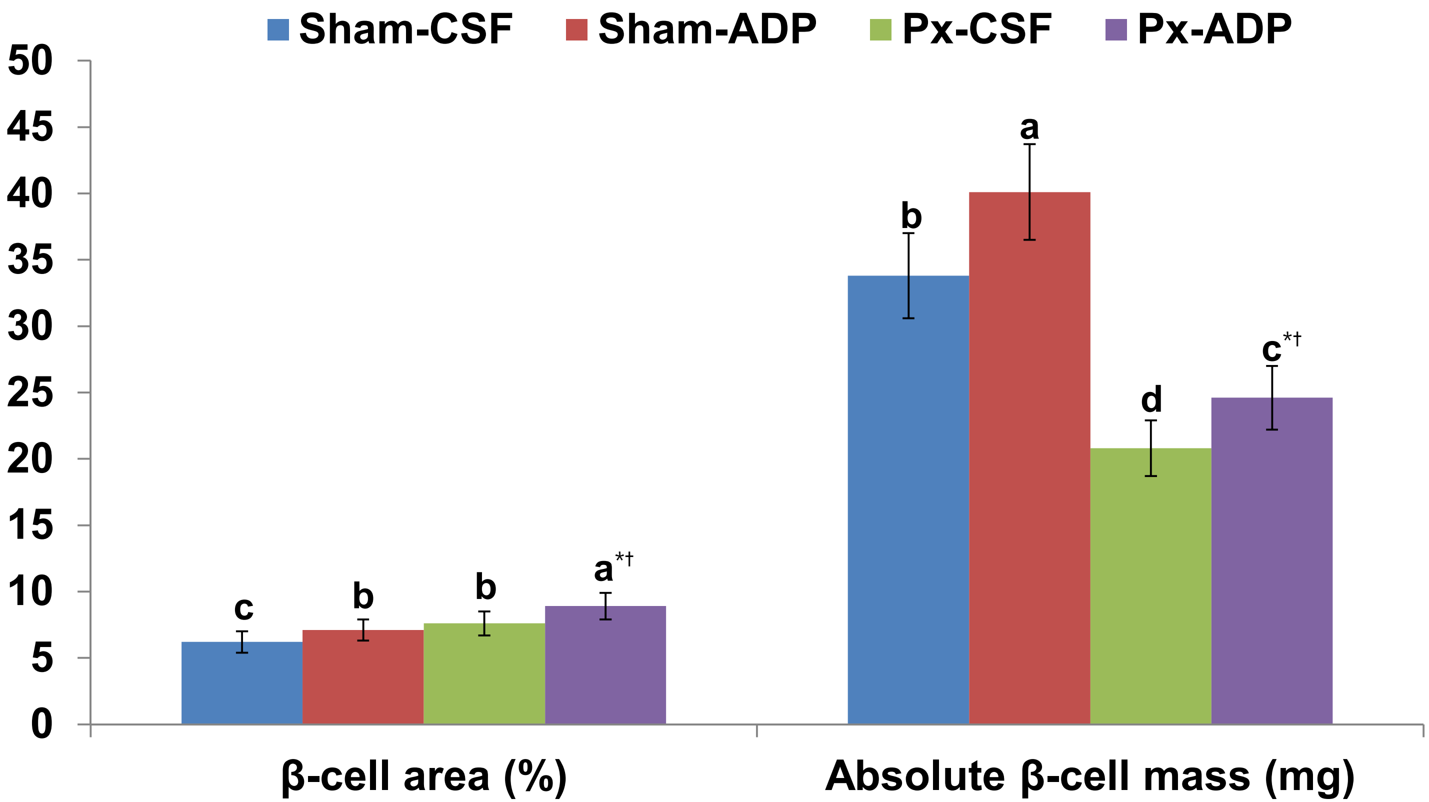
Insulin sensitivity at hyperglycemic state



*Significant effect of adiponectin (ADP) at p<0.05.
†Significant effect of diabetic status at p<0.05.

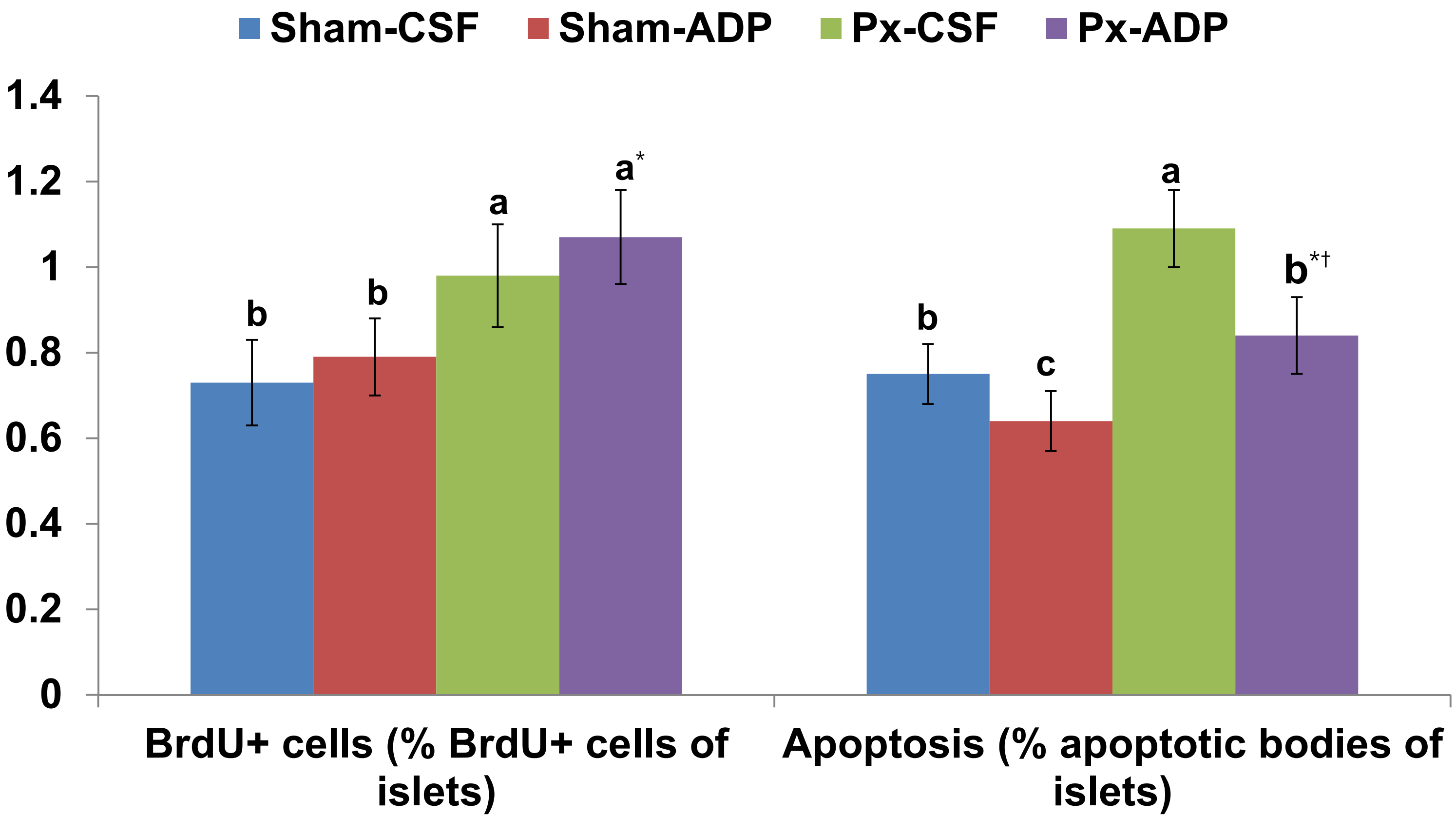
β-cell area and mass



*Significant effect of adiponectin (ADP) at $p<0.05$.

†Significant effect of diabetic status at $p<0.05$.

β-cell proliferation and apoptosis



*Significant effect of adiponectin (ADP) at $p<0.05$.
†Significant effect of diabetic status at $p<0.05$.

Summary

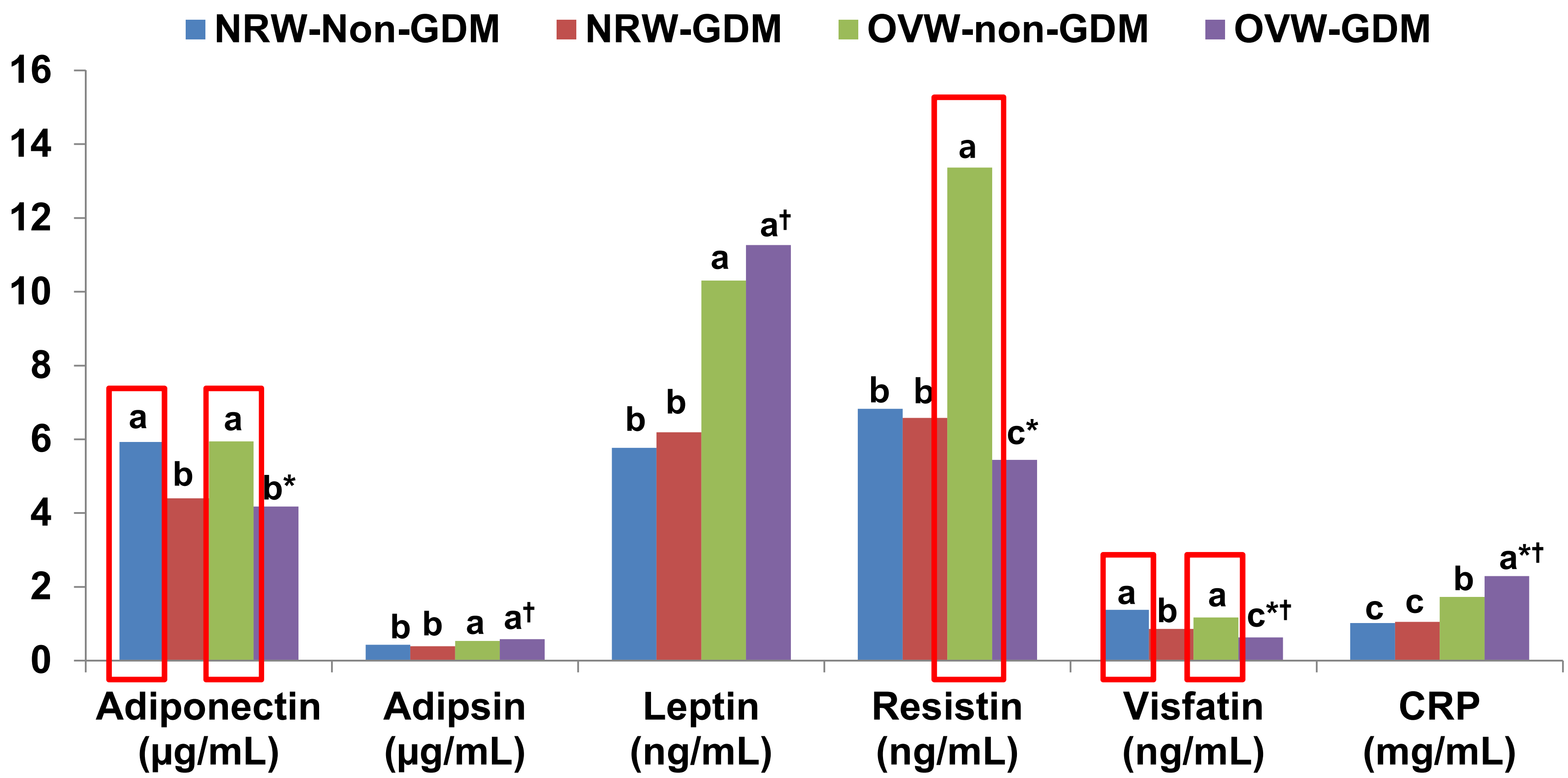
- Central adiponectin did not improve β-cell function but it increases β-cell mass by decreasing β-cell death.
- Central adiponectin also enhanced insulin sensitivity at hyperglycemic state.

Serum adipokines in GDM patients

Glucose Profiles

	Normal weight (BMI<23)		Overweight (BMI>=23)	
	Non-GDM (n=395)	**GDM (n=98)**	**Non-GDM (n=136)**	**GDM (n=117)**
Fasting Glucose (mg/dL)	78.8±5.4[c]	84.9±8.4[b]	80.2±4.9[bc]	92.8±12.4[a*†]
Glucose at 1 h after 50 g glucose (mg/dL)	111.0±14.7[b]	163.5±17.5[a]	113.1±14.4[b]	169.0±26.1[a*†]
Fasting Insulin (μU/mL)	11.6±5.6[c]	11.1±3.7[c]	12.8±5.8[b]	15.7±6.2[a*†]
HbA_{1C} (%)	5.3±0.3[b]	5.8±0.4[a]	5.4±0.4[b]	5.8±0.5[a*]
HOMA-IR	2.1±1.0[d]	2.3±0.9[c]	2.5±1.2[b]	3.6±1.6[a*†]
HOMA-B	293.7±229.2[a]	197.7±86.6[b]	288.7±153.5[a]	219.1±129.9[b*]

Circulating adipokine profiles



*Significantly different by gestational diabetes (GDM) at P<0.05

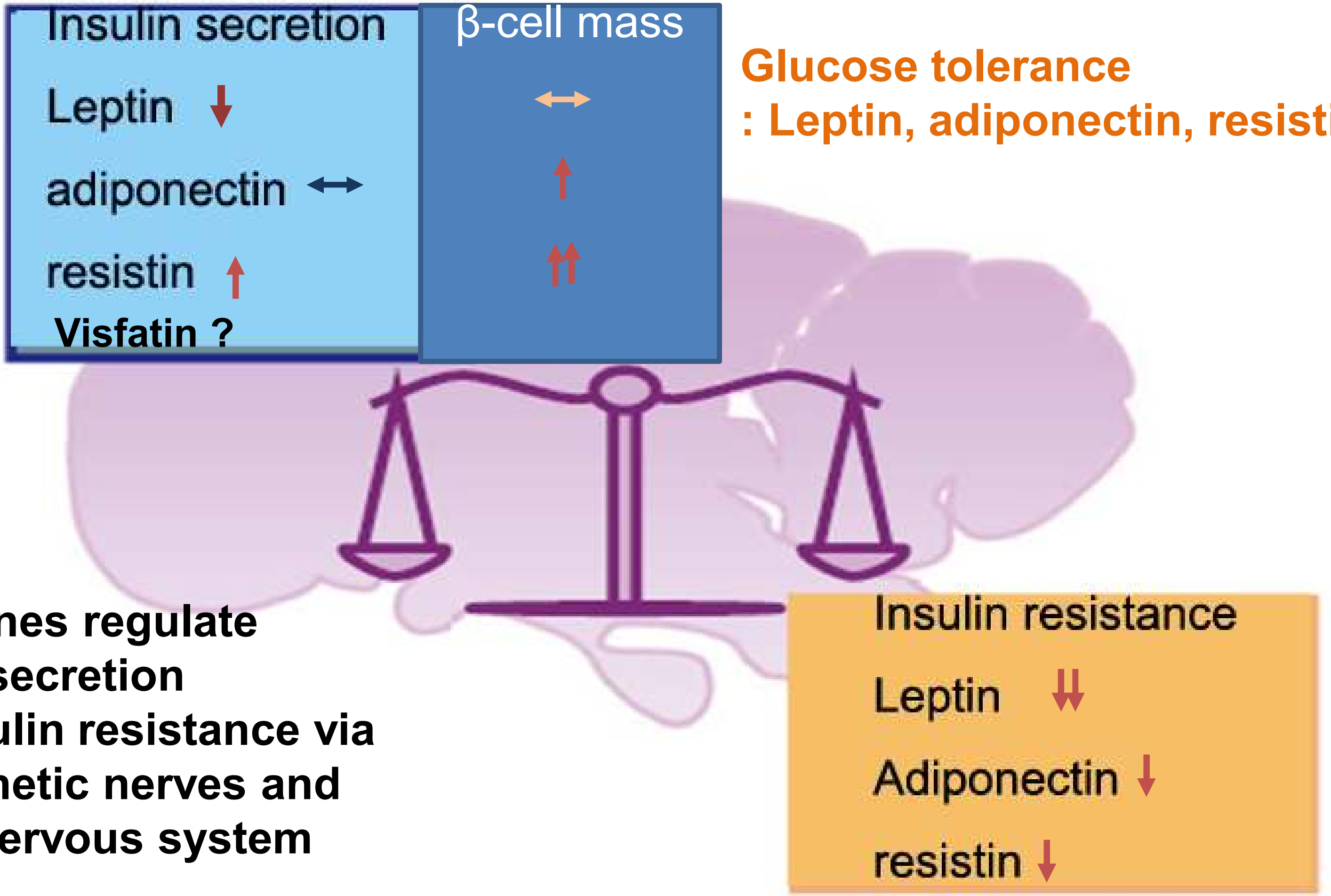
†Significantly different by body mass index (BMI) at P<0.05

a,b,cMeans in the same row with different superscripts were significantly different

Conclusions

Adipokines regulates β-cell function and mass as well as insulin sensitivity through several signal pathways including autonomic nervous system.

Roles of adipokines
- glucose homeostasis in diabetic rats

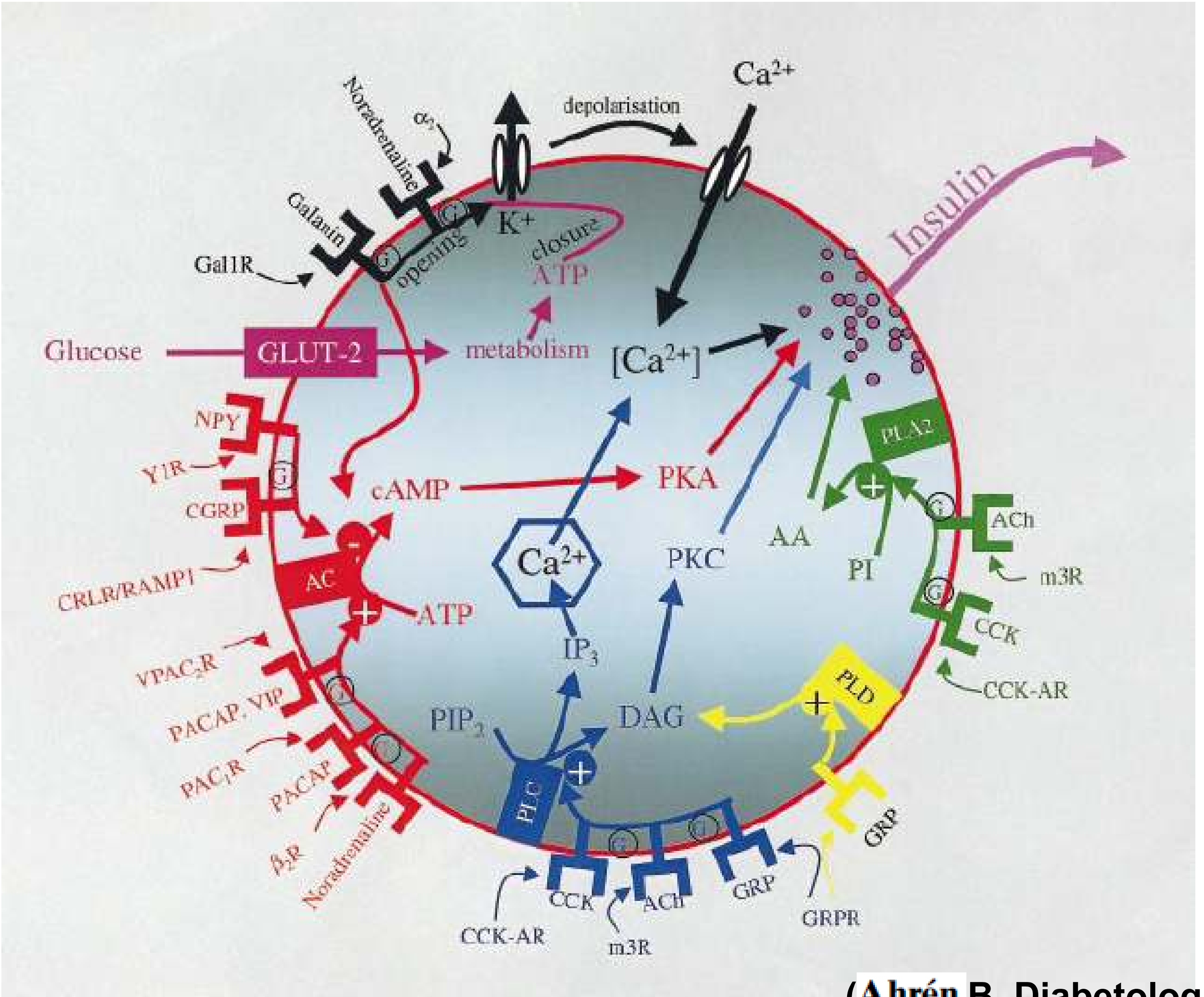


Visfatin ?

Glucose tolerance
: Leptin, adiponectin, resistin similar

Adipokines regulate insulin secretion and insulin resistance via sympathetic nerves and vagus nervous system

Possible sympathetic and parasymthathetic neural pathways to stimulate insulin secretion



(Ahrén B. Diabetologia, 2000)