Tiermodelle für die Erforschung von Ess-Störungen

Focus Übergewicht
– und was man dagegen tun kann

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Animal models of eating disorders

- DIO/DR
- Sex differences in eating controls
- Anorexia nervosa
- Binge eating

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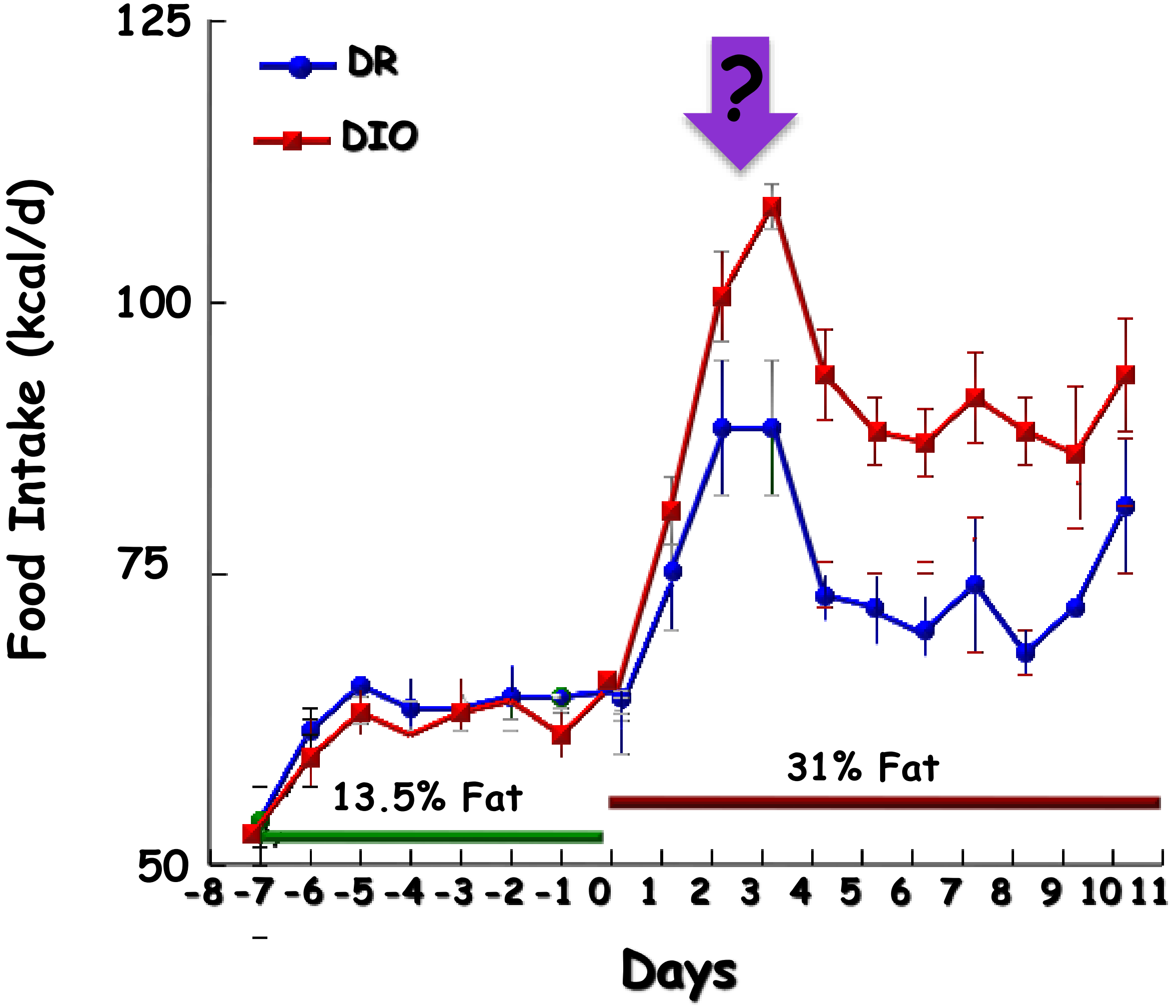
Model name	Mutation	Hyperphagia	Decreased Energy Expenditure	Hyperglycemia	Insulin Resistance
MONOGENIC MUTATIONS IN THE LEPTIN PATHWAY					
Leptin and its receptor					
Obesity models with a deficit downstream of the brain leptin receptor (e.g., POMC, MC4 receptor, etc.)					
OTHER MONOGENIC MODELS					
DIET-INDUCED MODELS; POLYGENIC MODELS					
OTHER GENETICALLY ENGINEERED MUTANTS					
SURGICAL OR CHEMICAL MODELS OF OBESITY					
SEASONAL MODELS OF OBESITY					
OTHER MODELS OF OBESITY AND ASSOCIATED METABOLIC CHANGES					

Overview of animal models of obesity
Lutz TA, Woods SC
Curr Protoc Pharmacol. 2012; chapter 5: Unit 5.61

DIO and DR rats

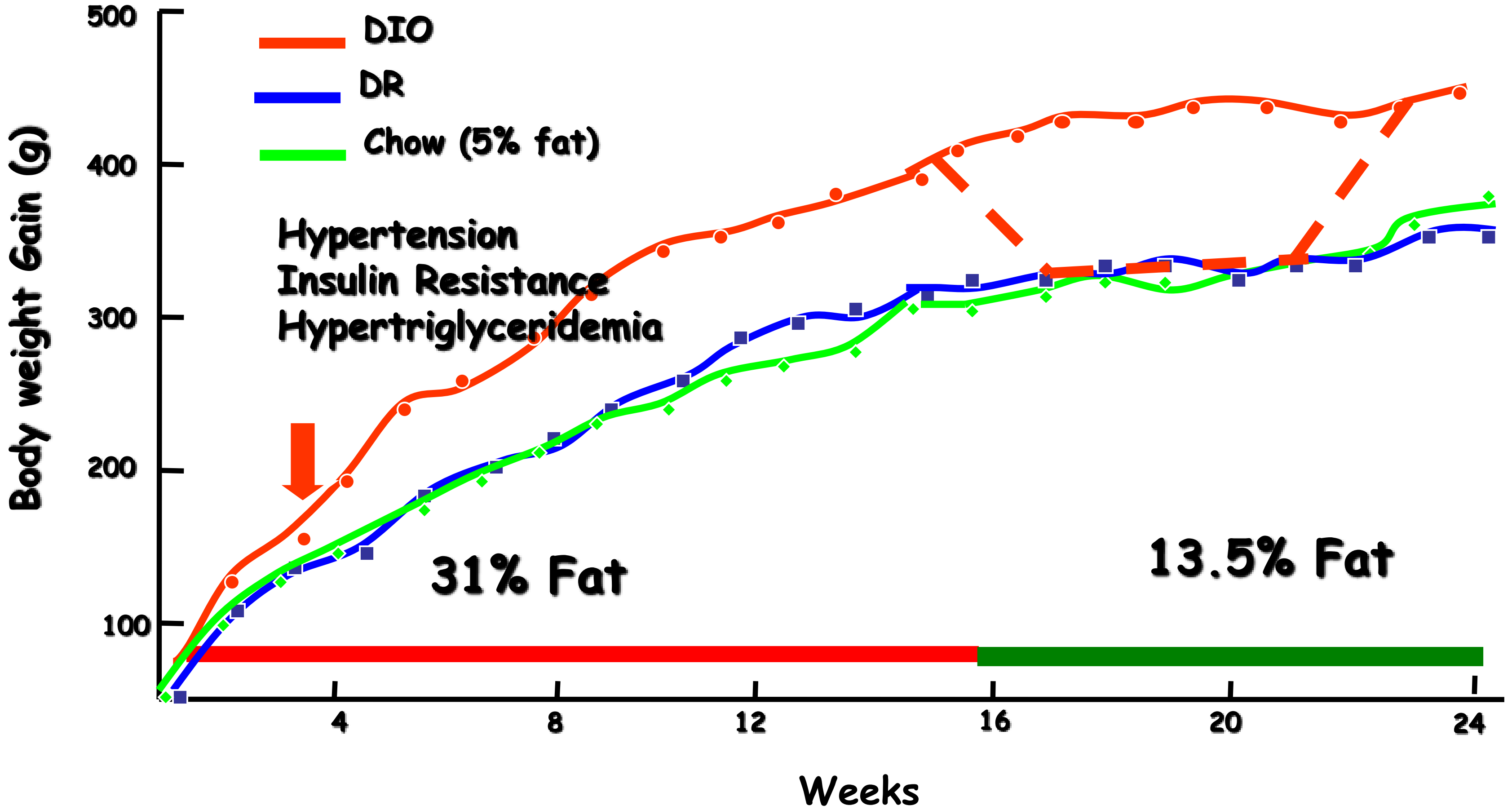
- **Selectively bred from a outbred rat population.**
- **On low fat (13.5%) chow diet, DIO and DR rats have the same amount of carcass fat.**
- **On low fat diet, DIO rats are bigger than DR rats.**
- **When put on 31.5% fat diet, DIO [but not DR] rats become hyperphagic and obese, leptin and insulin-resistant.**
- **The DIO phenotype is inherited in a *polygenic* fashion.**

DIO rats do not correct adequately for increased fat in their diet



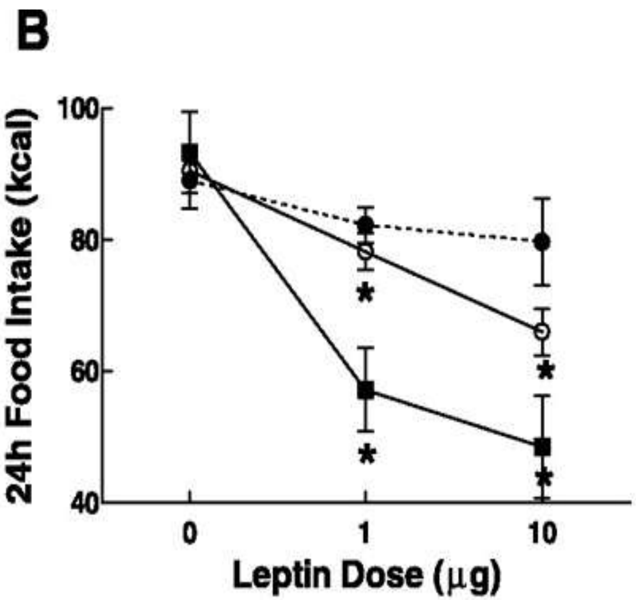
Levin et al, AJP 285:E949, 2003

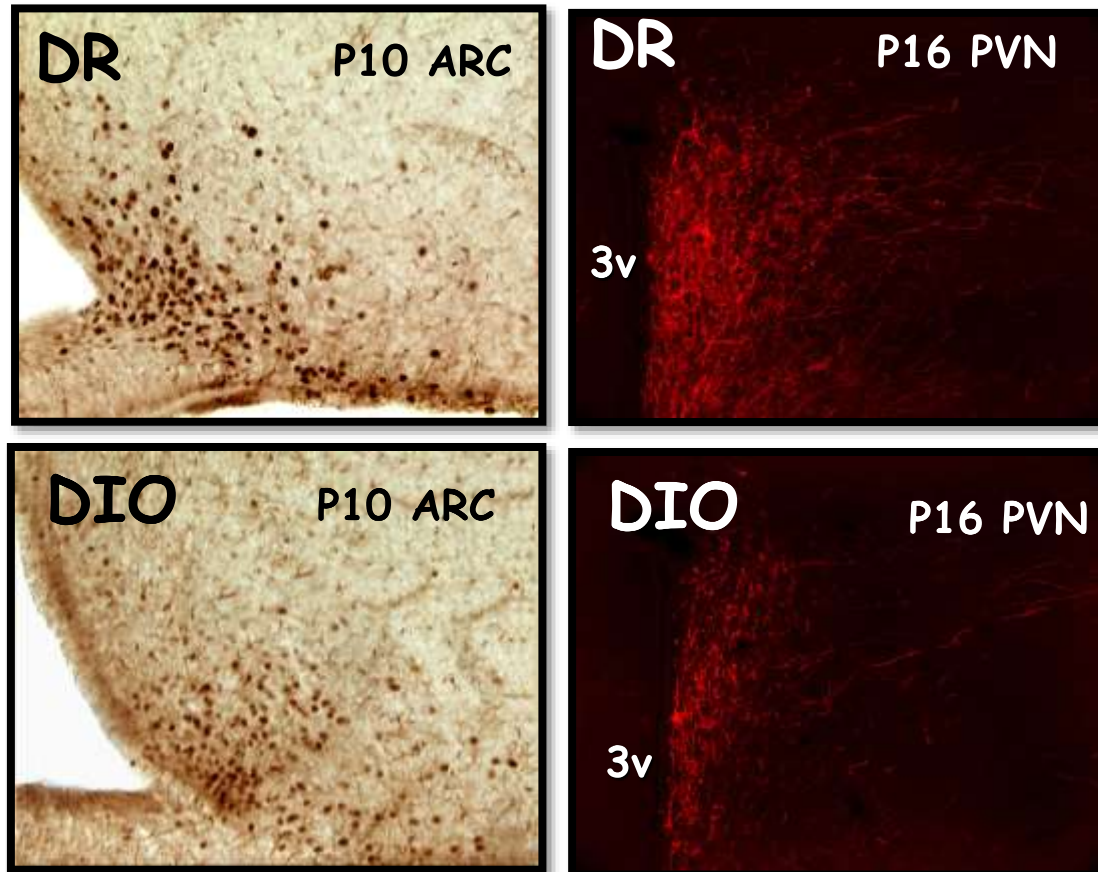
Body weight gain under low and high fat diet



Levin et al, 2003

DIO rats have reduced leptin (and insulin) sensitivity before they become obese





In dogs:
Broussard et al. Insulin access to skeletal muscle is impaired during the early stages of diet-induced obesity.Obesity, 2016 doi: 10.1002/oby.21562.

Levin et al, 1997, 2003, 2007
Bouret et al, 2008
Gorski et al, 2007

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Obesity in women

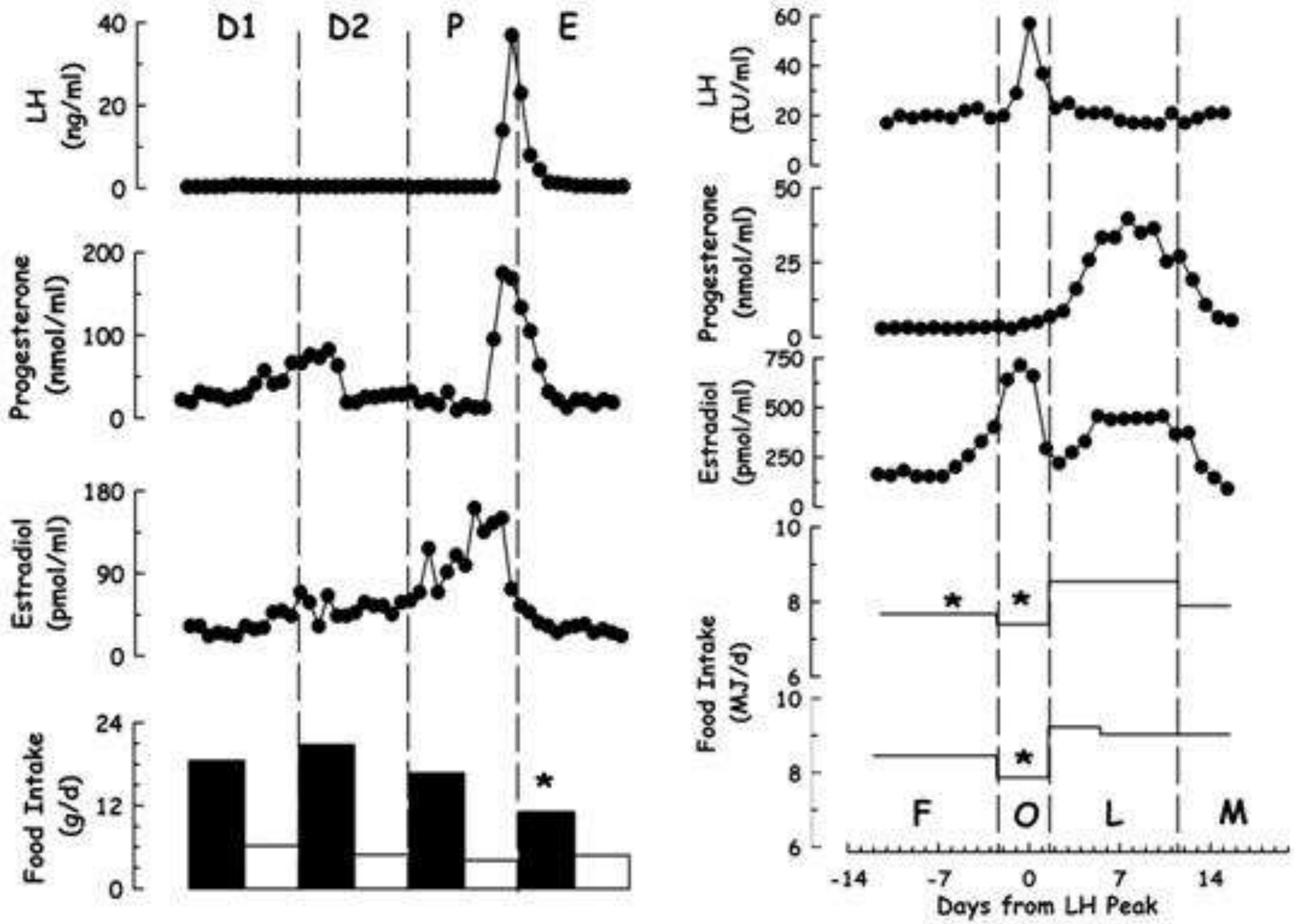
1. Loss of estradiol (surgical ovariectomy or menopause) leads to increases in adiposity

2. There is a sex difference in obesity: more women are morbidly obese than men

3. There is a sex difference in number of gastric bypass surgical procedures:

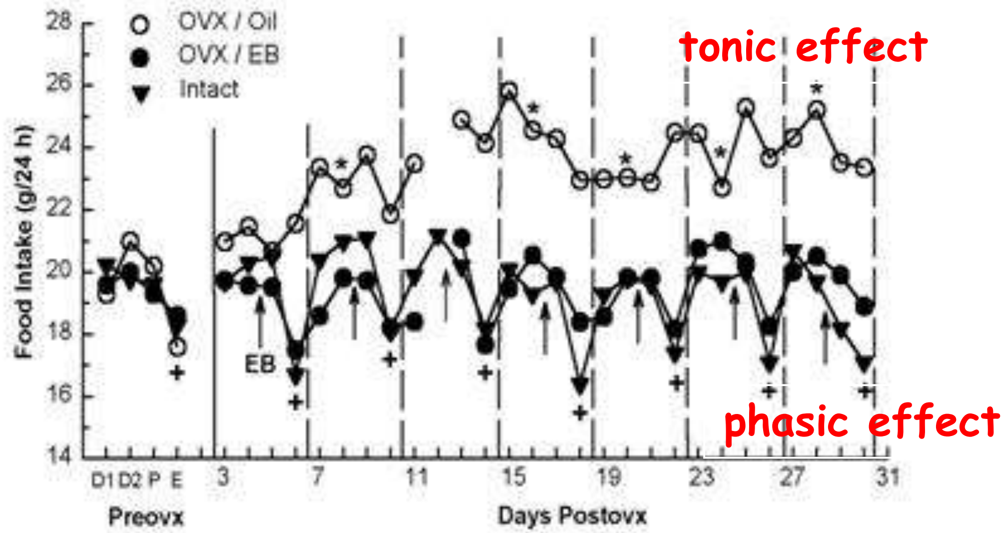
Population	Time interval						Trend *P* value
	1987–1989	1990–1992	1993–1995	1996–1998	1999–2001	2002–2004	
Gender							
Females, N = 35,178 (85)	3674 (88)	3687 (87)	5655 (86)	4750 (84)	9346 (85)	8606 (83)	<.0001
Males, N = 6,142 (15)	506 (12)	539 (13)	889 (14)	900 (16)	1605 (15)	1703 (17)	

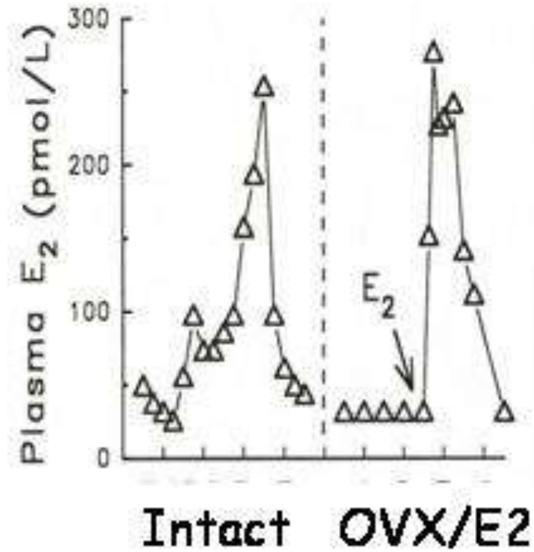
In females, eating decreases during the peri-ovulatory phase of the ovarian cycle (estrus)

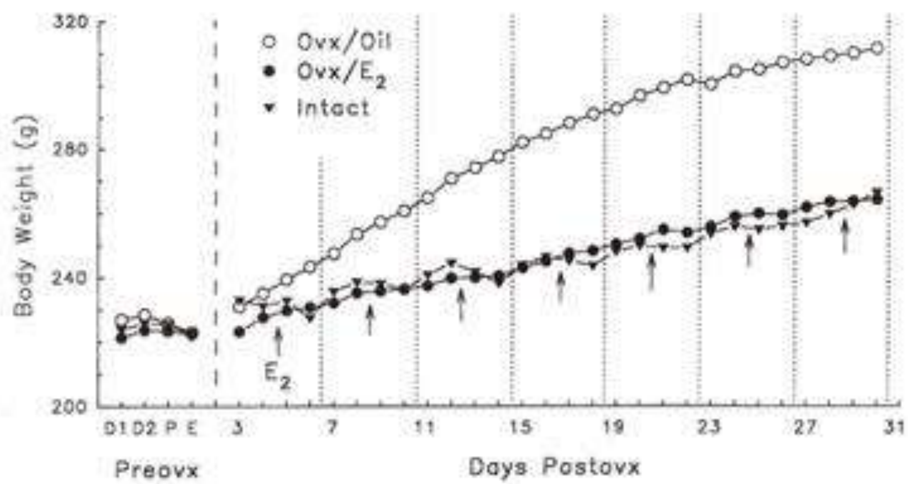


Geary et al., 2004

Estradiol is sufficient to normalize food intake & body weight in ovariectomized (OVX) rats







Asarian & Geary, 2002

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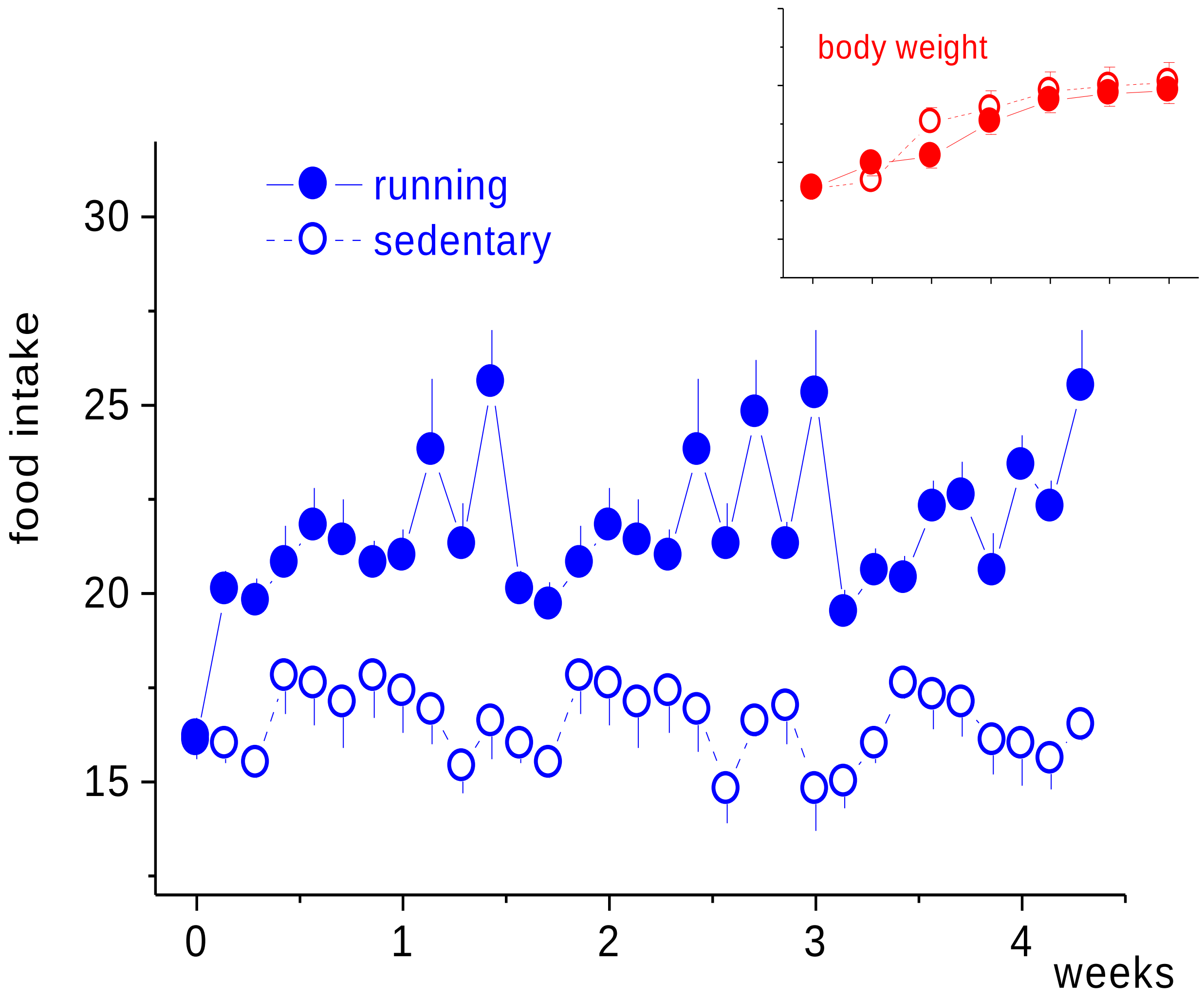
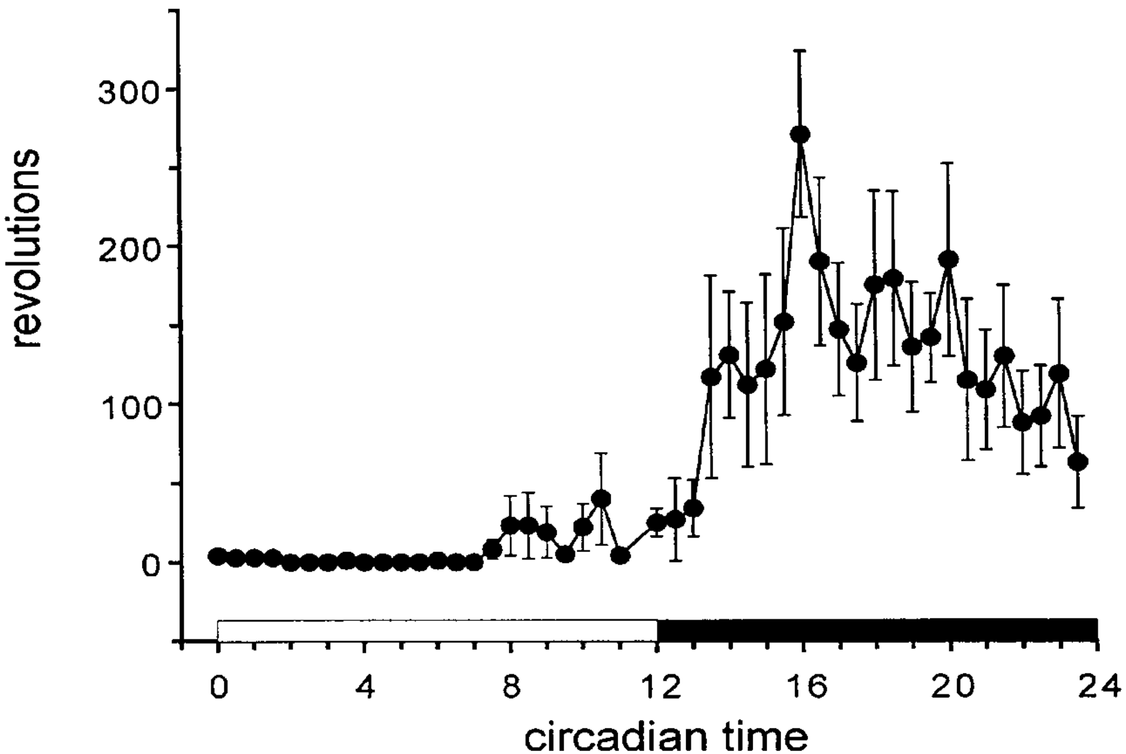
body weight homeostasis

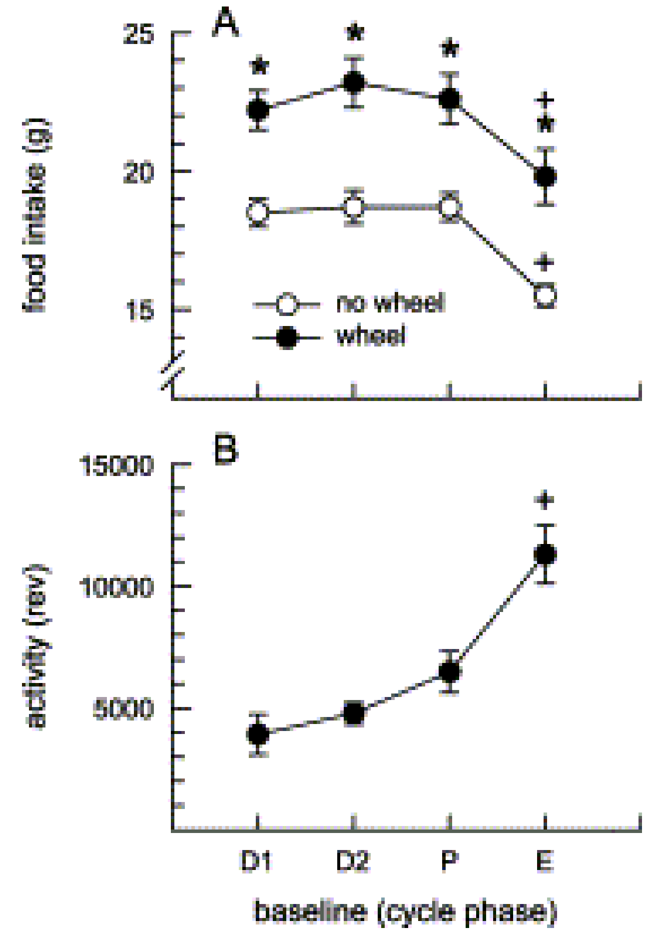
increased food intake during exercise



Anton Scheurink; by courtesy

Voluntary running activity: 5 km/day (females in estrus: > 20 km/day)

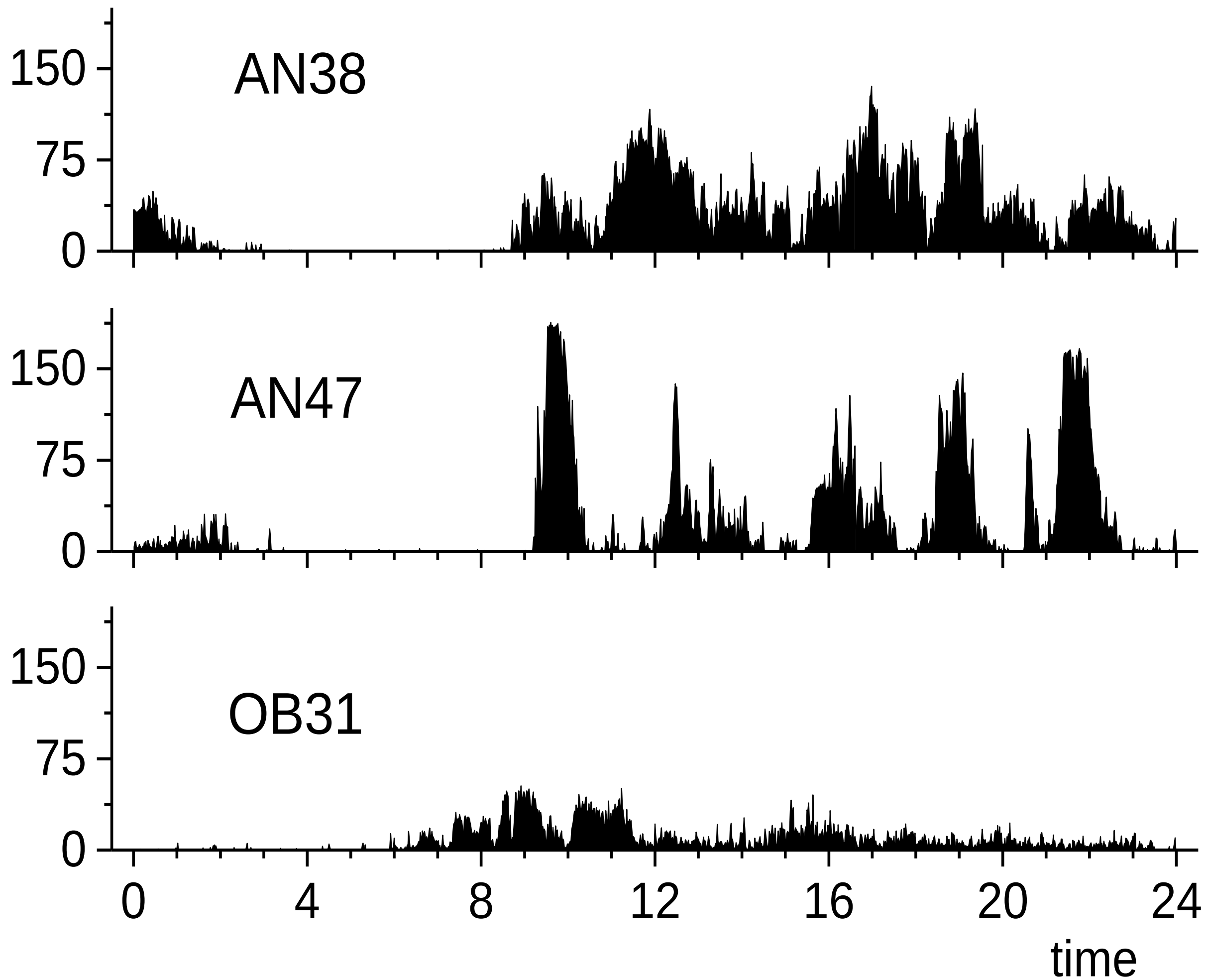




Anton Scheurink; by courtesy

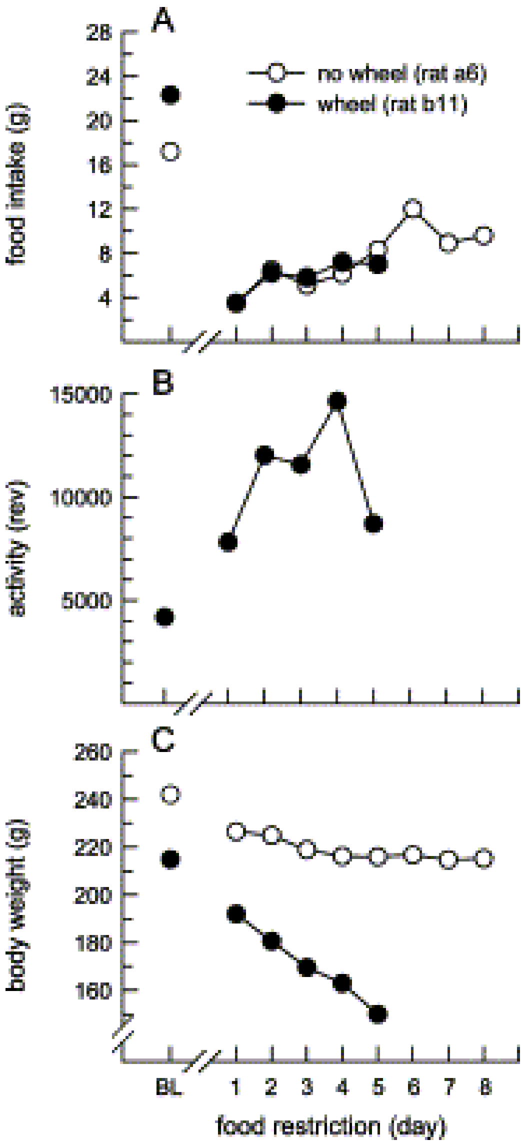
Dixon et al., 2003

Hyperactivity in anorexia nervosa



Anton Scheurink; by courtesy

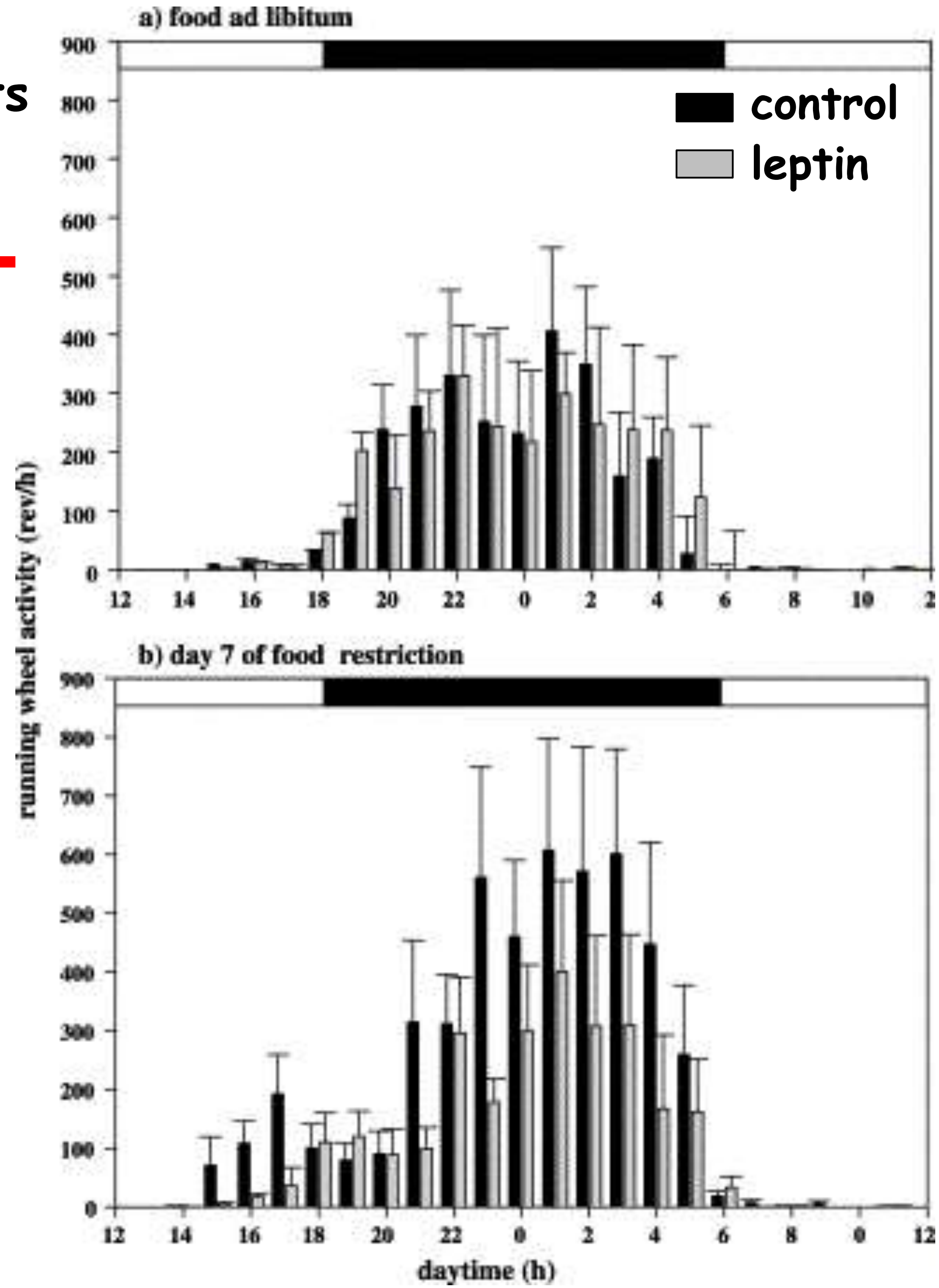
Effect of food restriction and wheel running activity on BW and estrus cycle



	Rats with wheels	Rats without wheels
Daily food intake (g)	8.2±0.9	7.9±0.2
Food intake suppression (% of baseline)	62.7±4.25	55.1±1.2
Total body weight loss (g)	54.2±4.3[a]	21.3±2.8
Body weight suppression (% of baseline)	24.1±2.3[b]	10.0±1.1
Daily activity (revolution)	8186±739[c]	-
Increase in activity (% of baseline)	23.6	-
Disruption in estrous cyclicity (%)	100	0

Dixon et al., 2003

Leptin decreases hyperactivity in severely food restricted rats (60% of ad lib intake for 7d) but not in ad libitum fed rats



Hebebrand et al., 2003
See also:
Hillebrand et al., 2008

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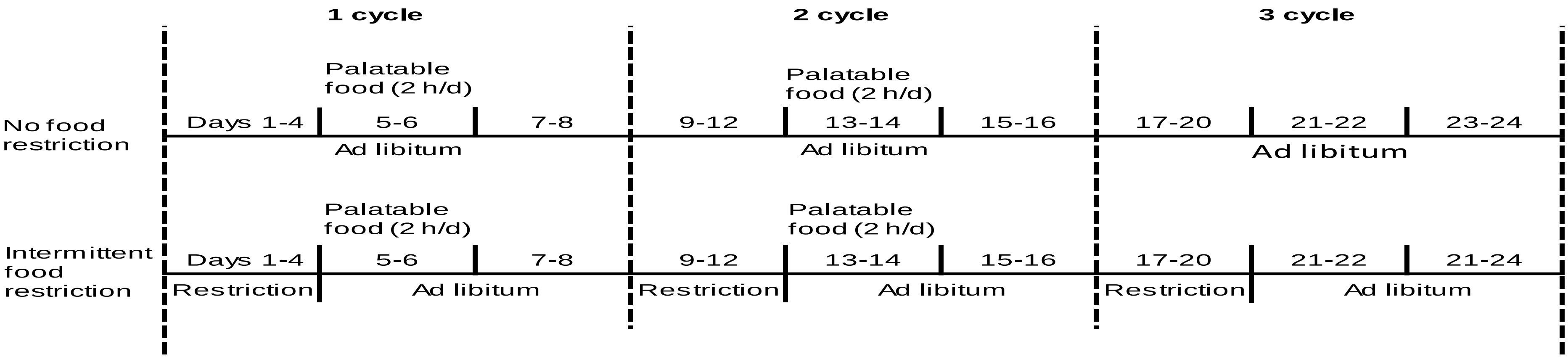
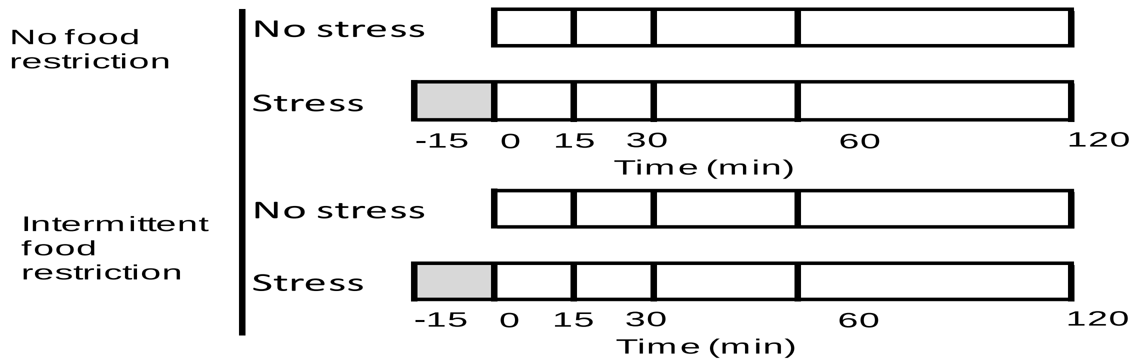
Binge eating model





Restriction: 66% of chow intake on days 1-4 and free-feeding on days 5-8 of each binge cycle

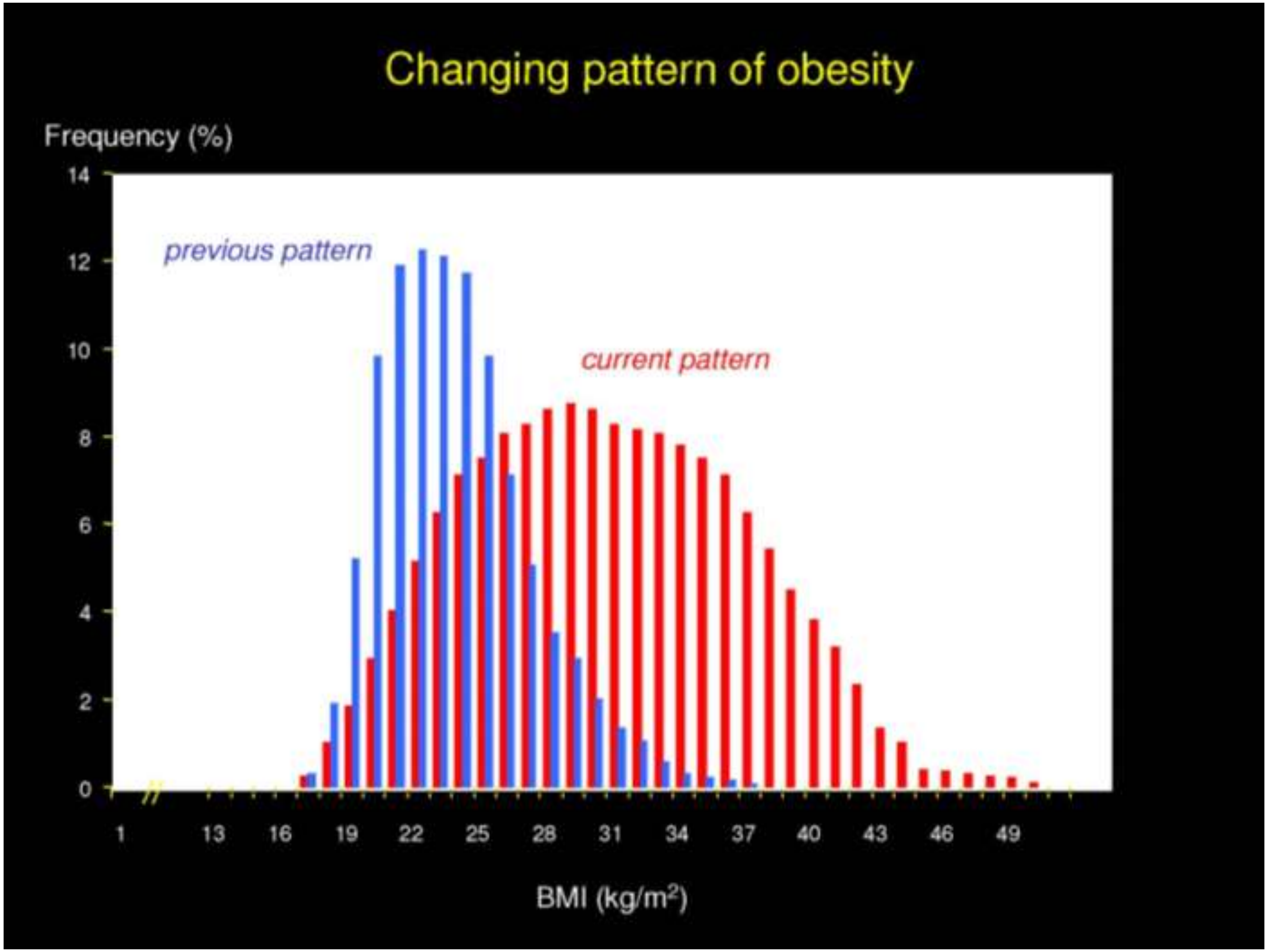
Frustration stress: presentation of (inaccessible) Nutella jar

Micioni di Bonaventura, in press

Estrogen attenuates binge eating response in female OVX rats

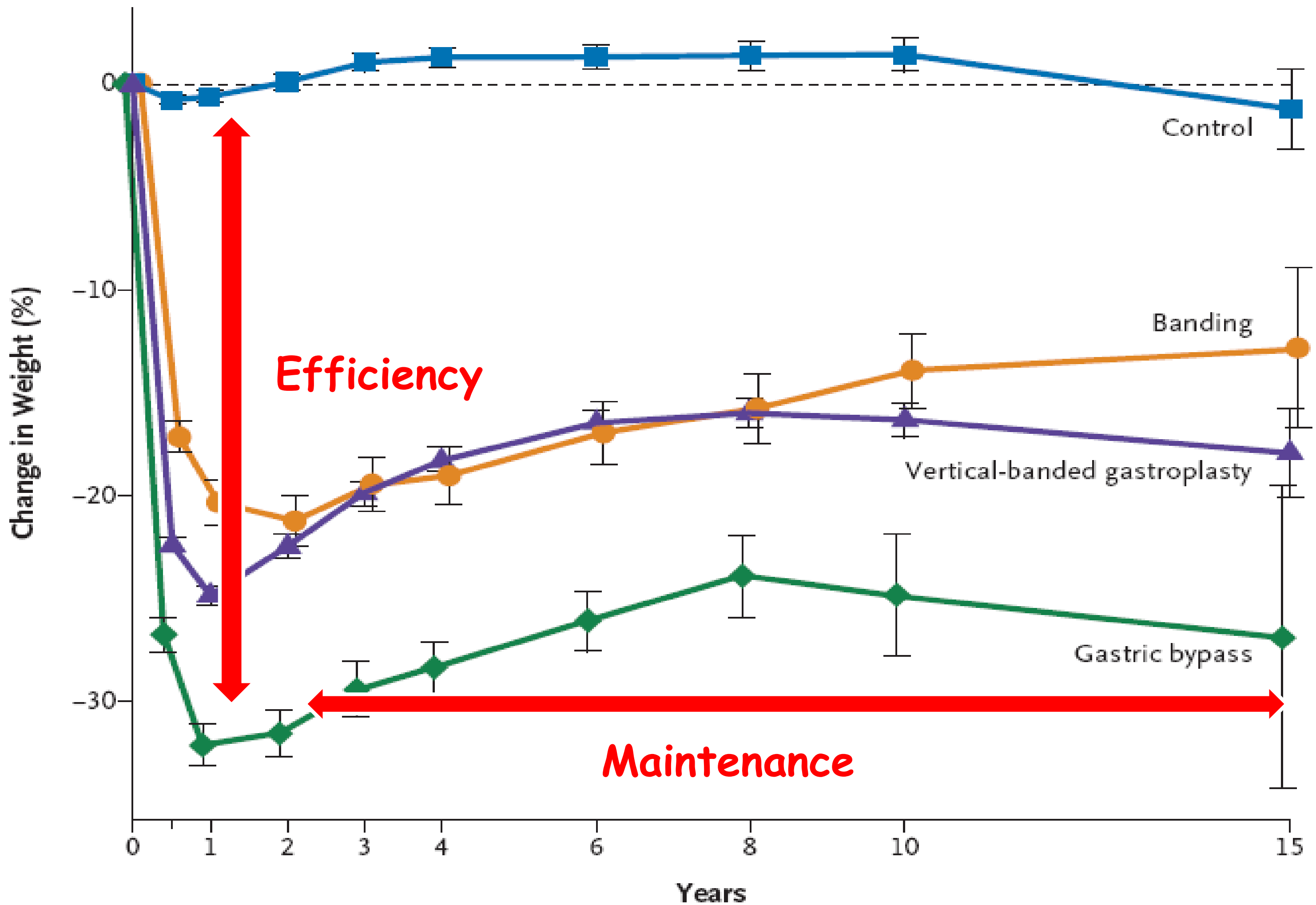
Micioni di Bonaventura, in press

Not only obesity, but the extent of obesity also increases



Farooqi and O'Rahilly, 2004

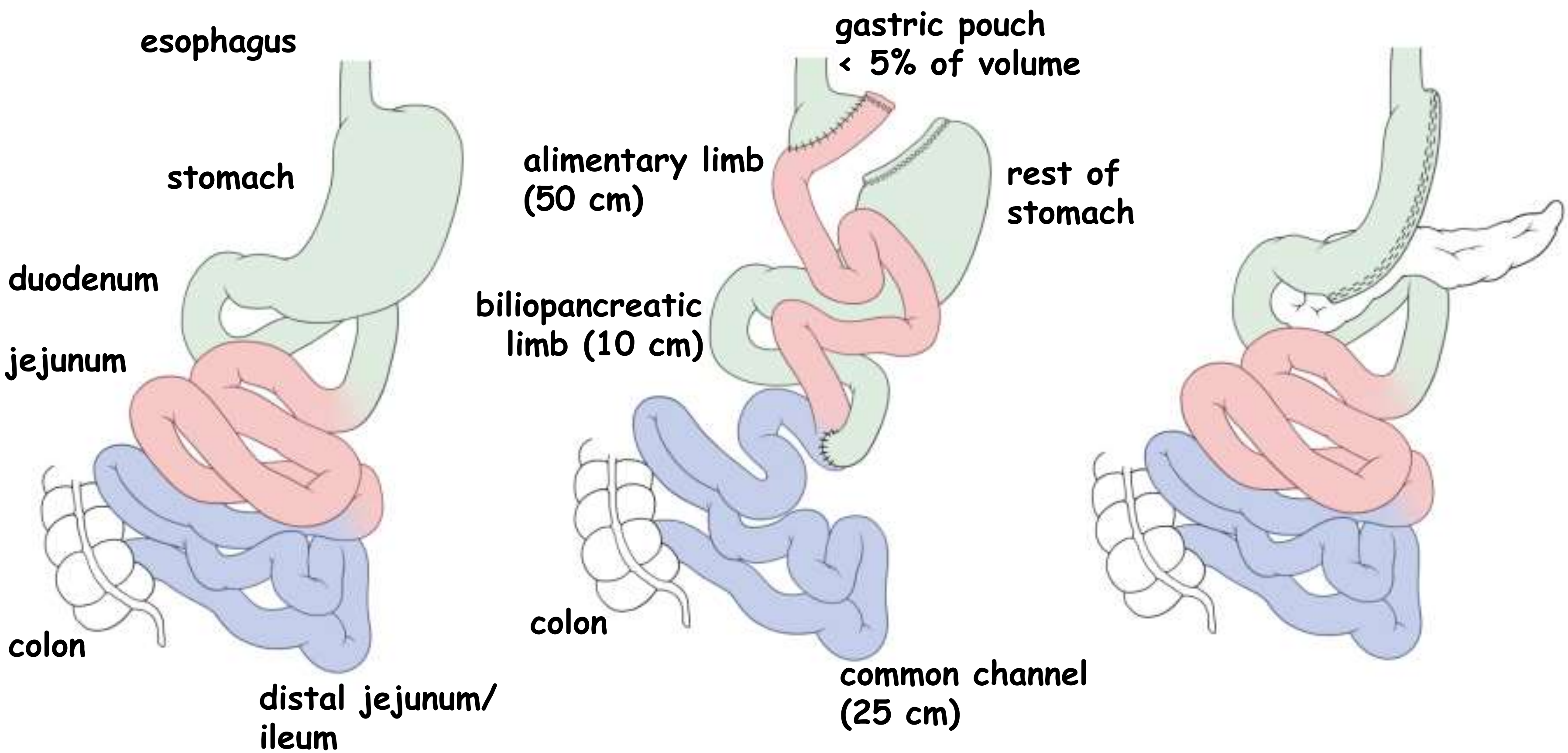
Efficient weight loss and maintenance after bariatric surgery, in particular RYGB



Sjöström et al. 2004

RYGB and VSG surgery

César Roux, 1857 - 1934

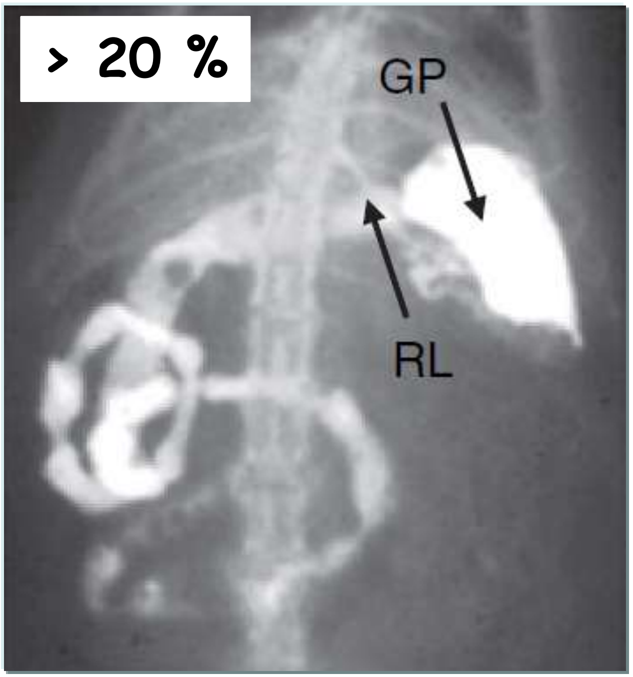


SHAM

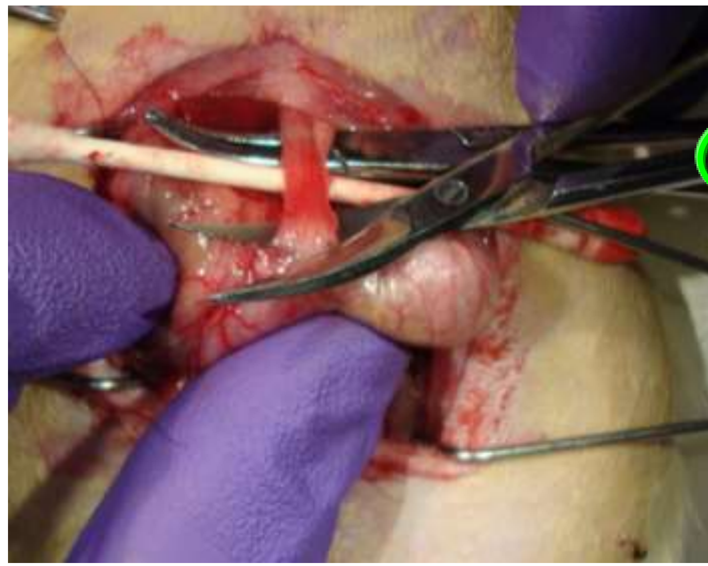
RYGB
Roux-en-Y
gastric bypass

VSG
Vertical
sleeve gastrectomy

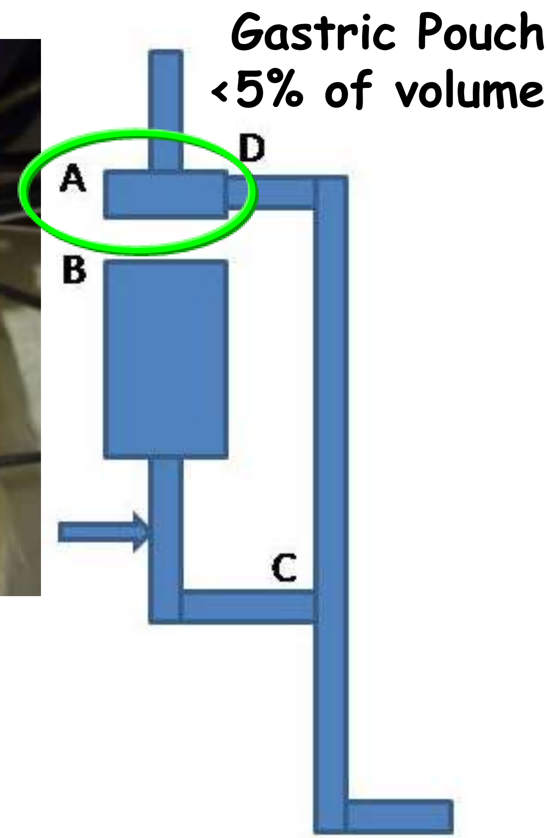
RYGB surgery



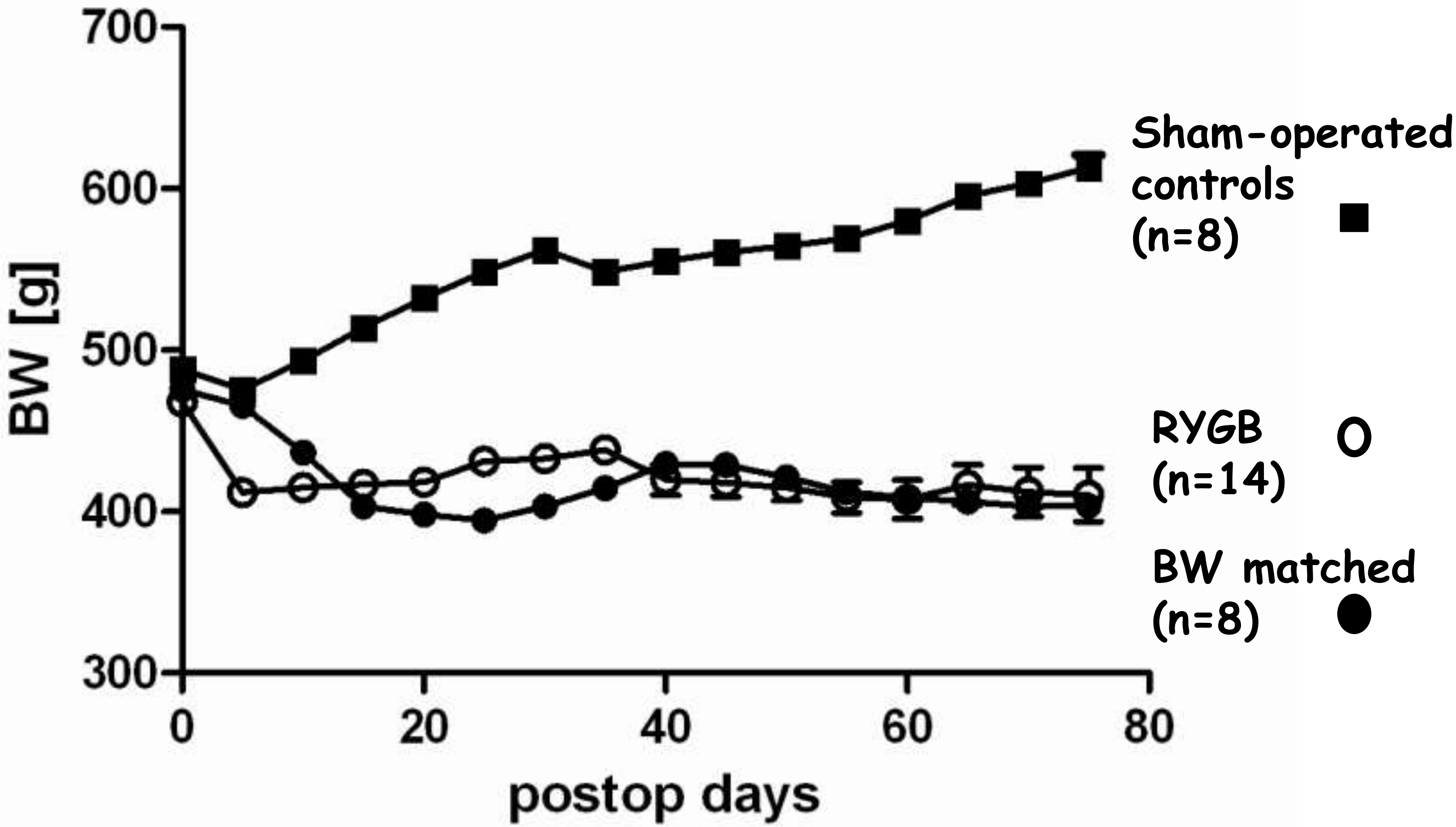
Stylopoulos et al., 2009



Bueter et al., 2010

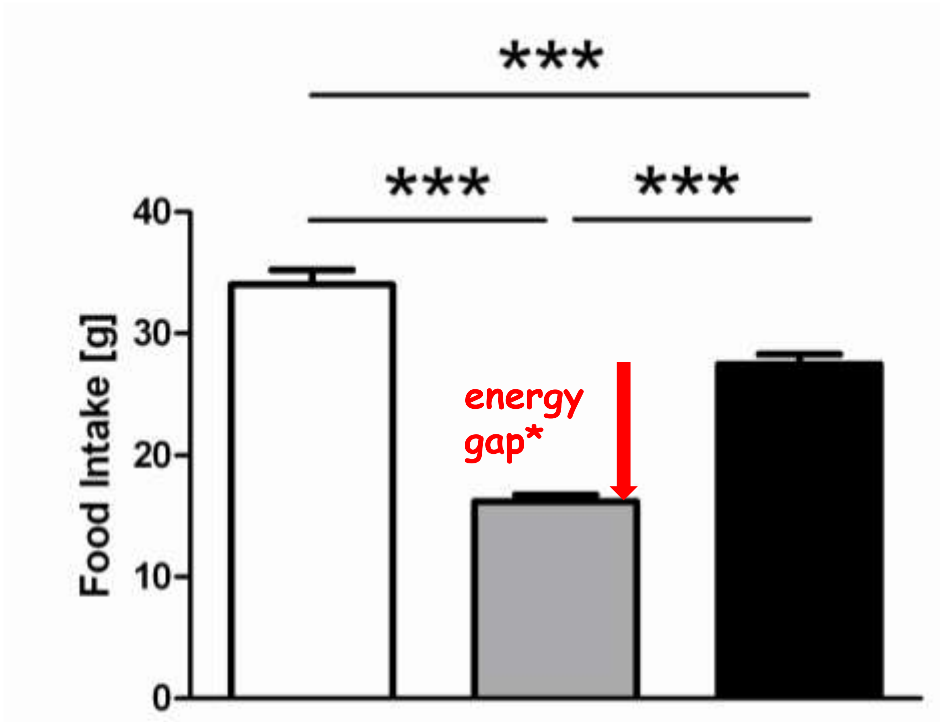


Development of body weight after surgery



Bueter et al., 2010

Spontaneous average food intake in SHAM and RYGB rats



* no significant alteration of fecal nutrient content

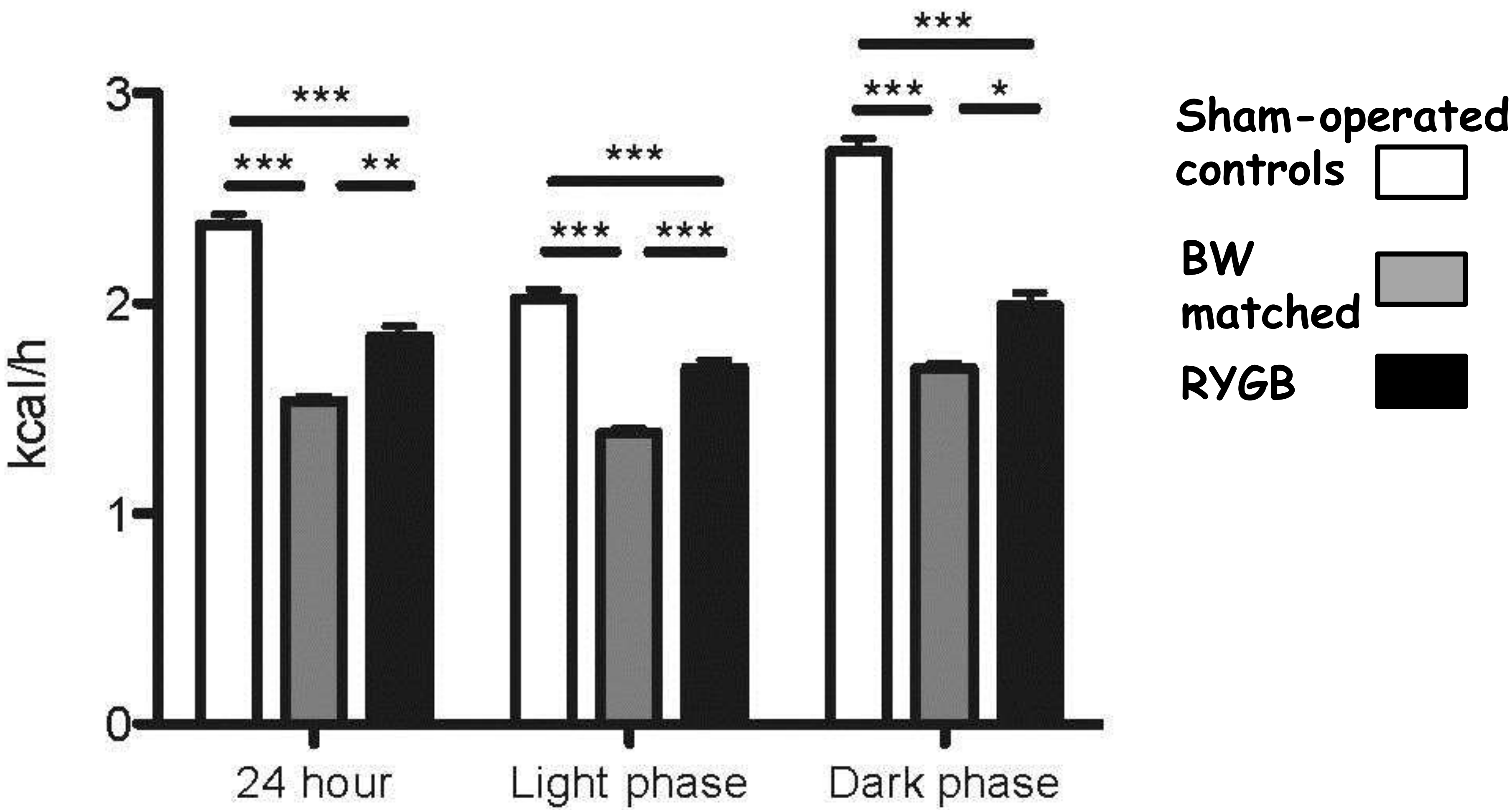
Sham-operated controls

BWM

RYGB

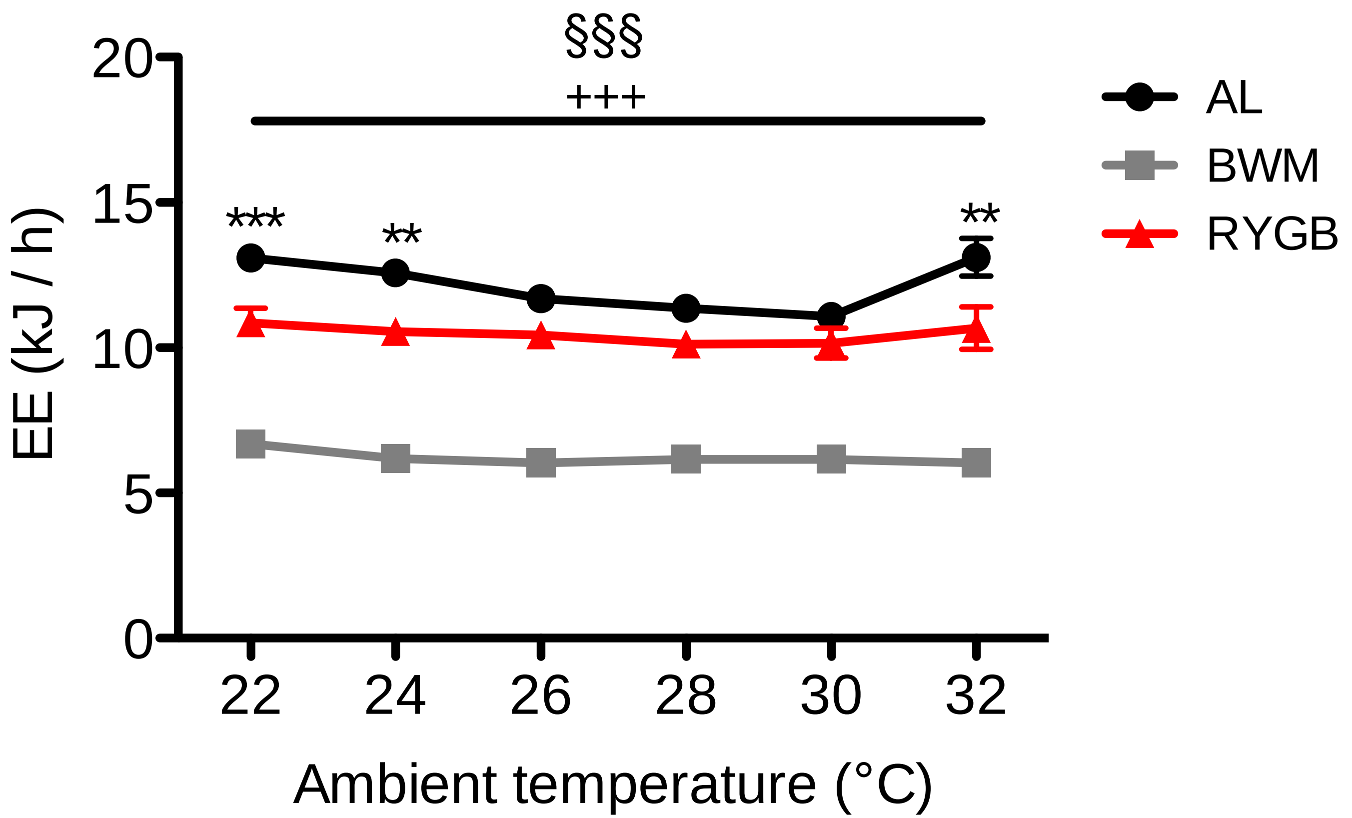
Bueter et al., 2010

Baseline energy expenditure in SHAM and RYGB rats

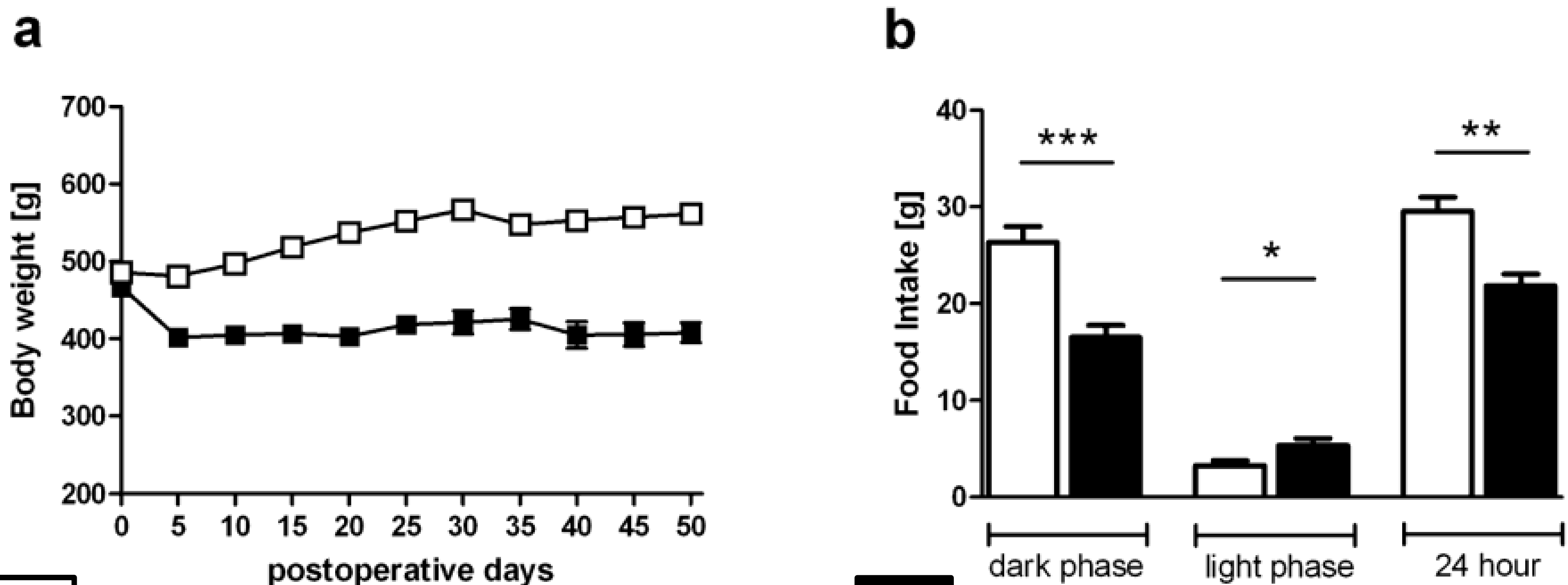


Bueter et al., 2010

Baseline energy expenditure in SHAM and RYGB rats at different ambient temperatures



Spontaneous average food intake in SHAM and RYGB rats

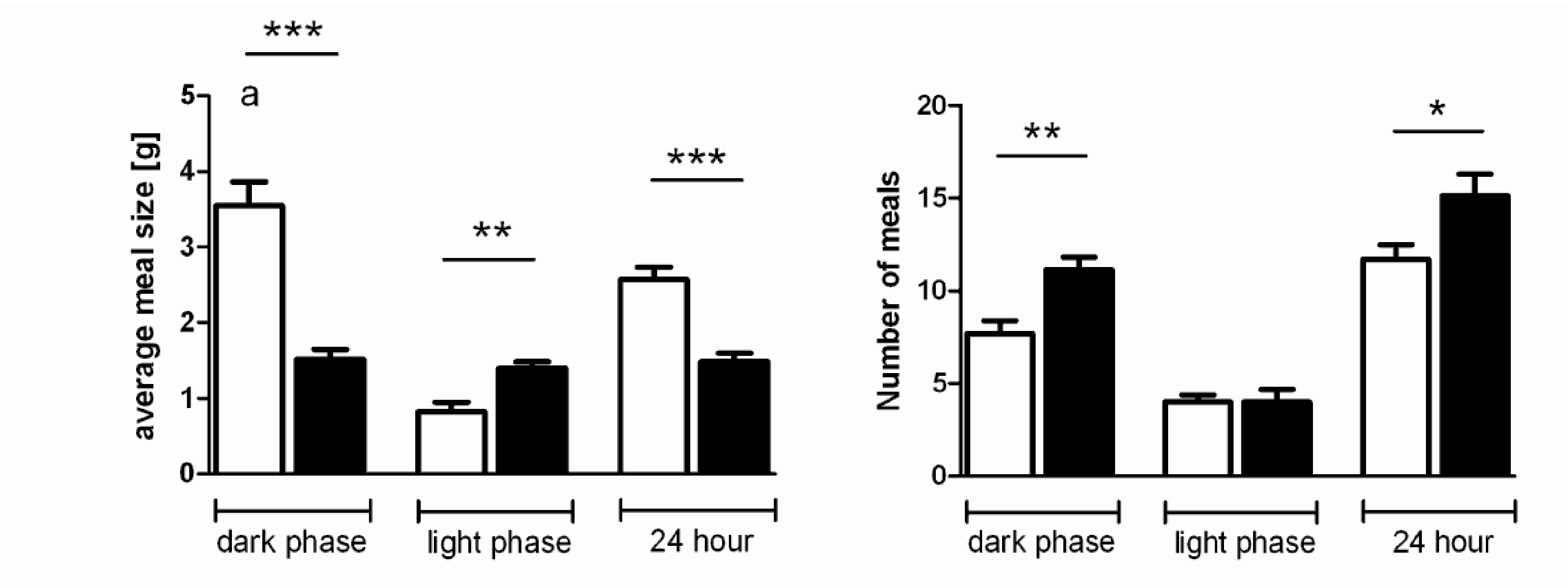


□ Sham-operated controls

■ RYGB

Bueter et al., 2010

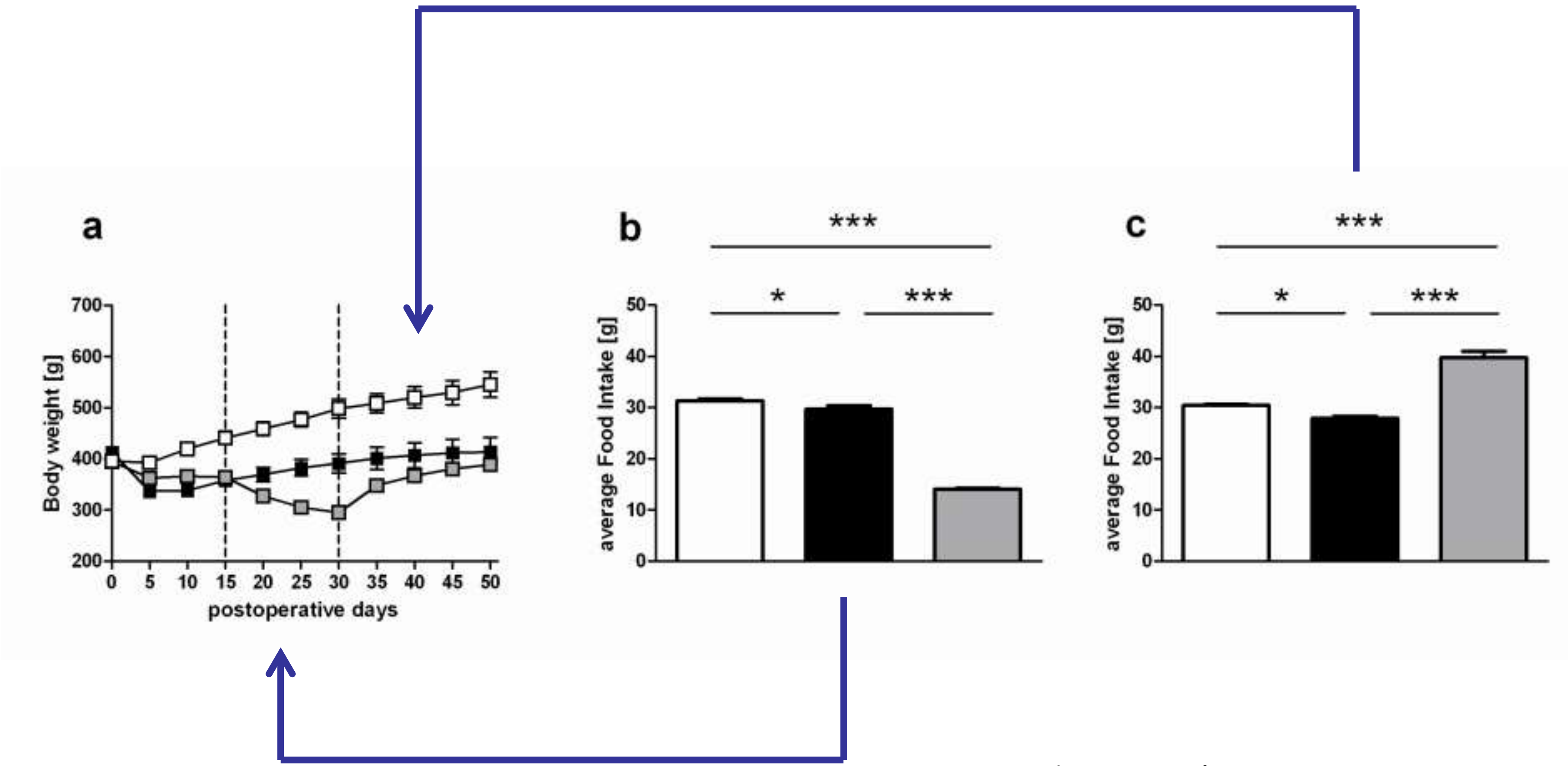
Meal pattern in SHAM and RYGB rats



Sham-operated controls

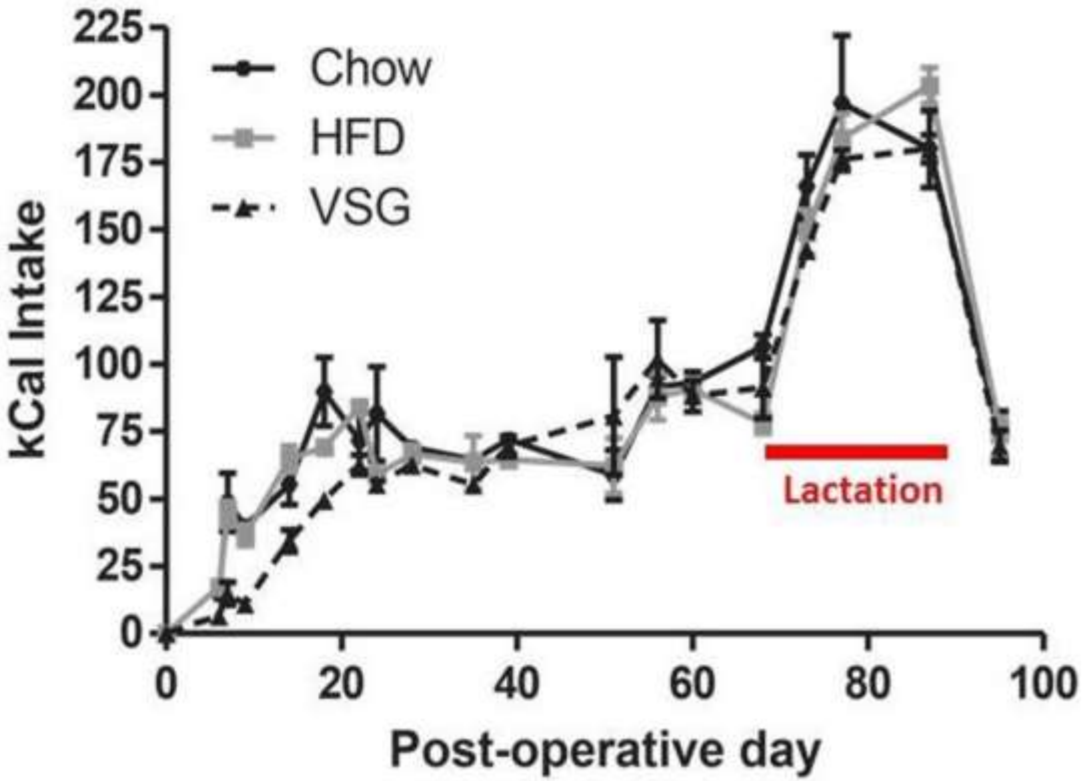
RYGB

Spontaneous average food intake in SHAM and RYGB rats: reduced eating is not primarily due to mechanical restriction*



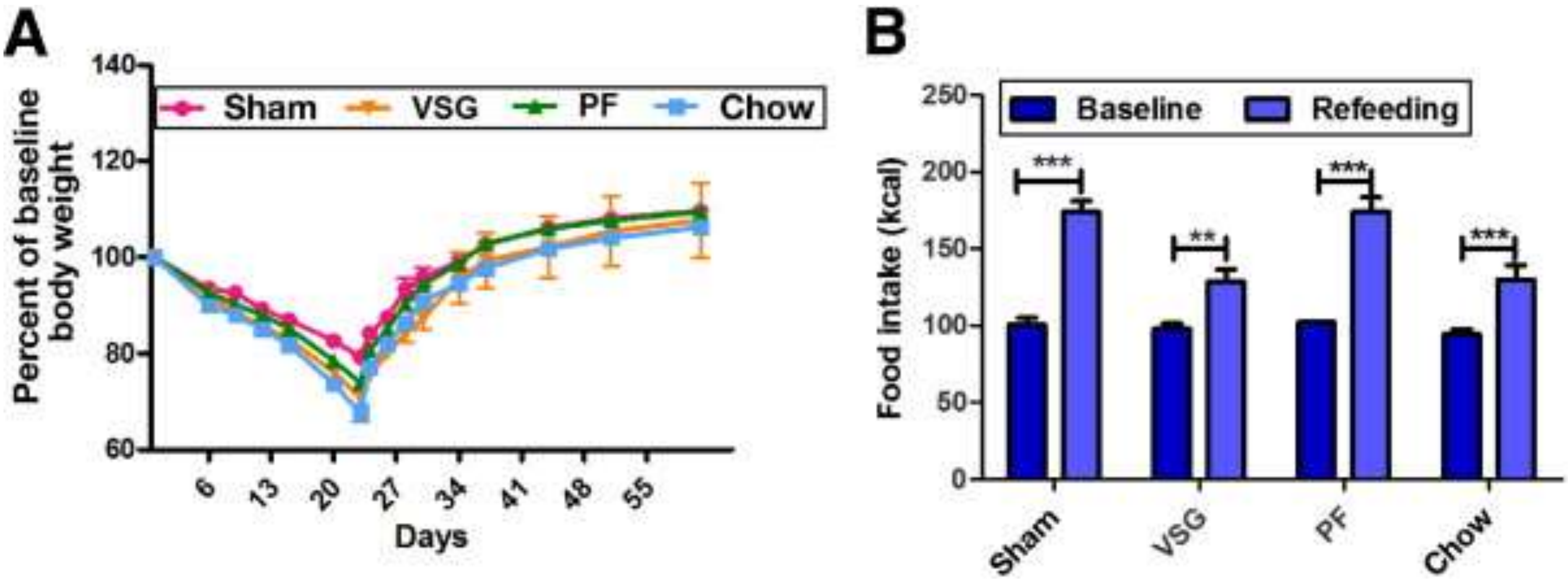
* See also:
no significant alteration of fecal nutrient content

Spontaneous average food intake in SHAM and VSG rats:
It is unlikely that reduced eating is primarily due to mechanical restriction



By curtosy: Adam Chambers

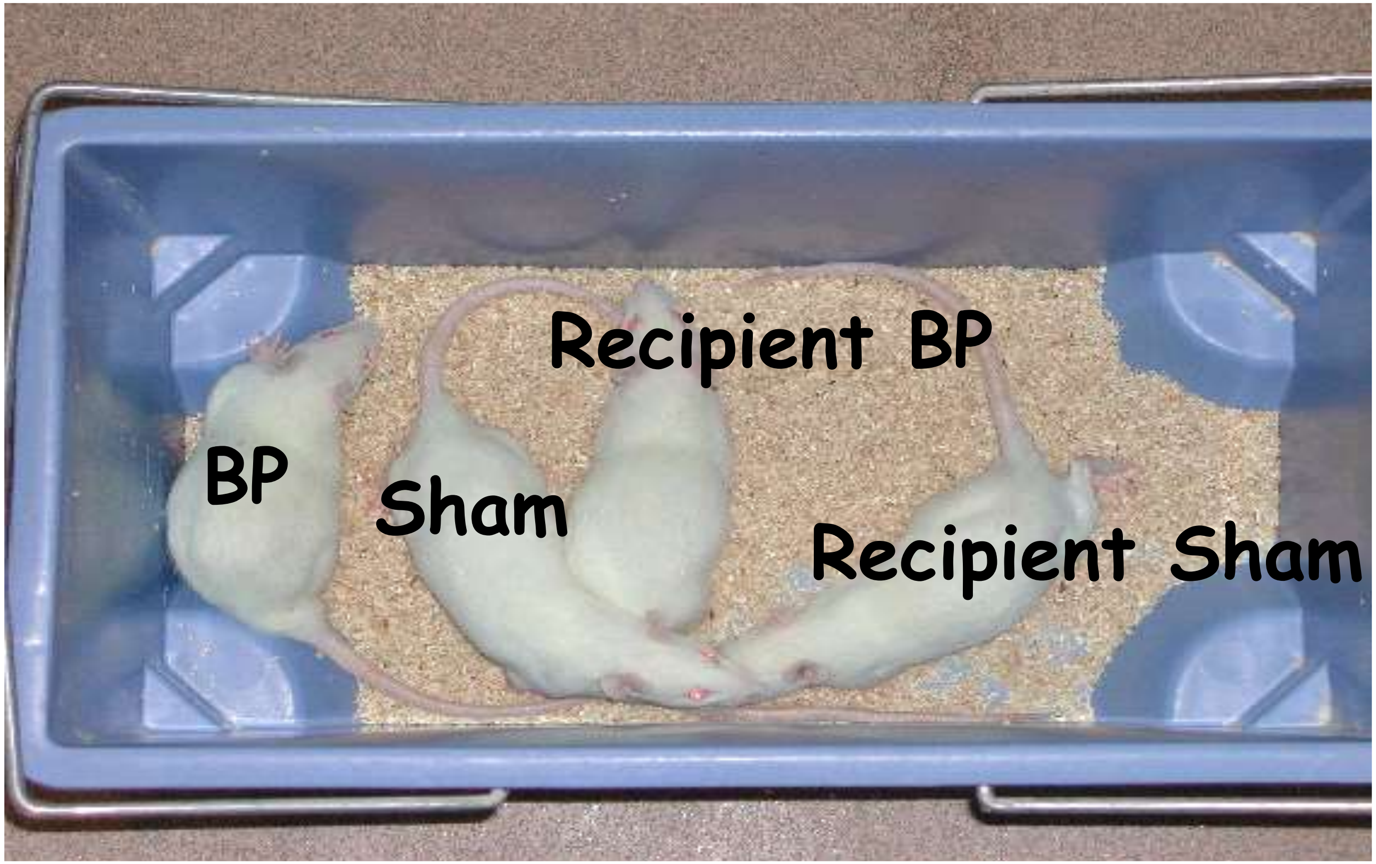
Spontaneous average food intake in SHAM and VSG rats: It is unlikely that reduced eating is primarily due to mechanical restriction



Food restriction to 73% for 22 days

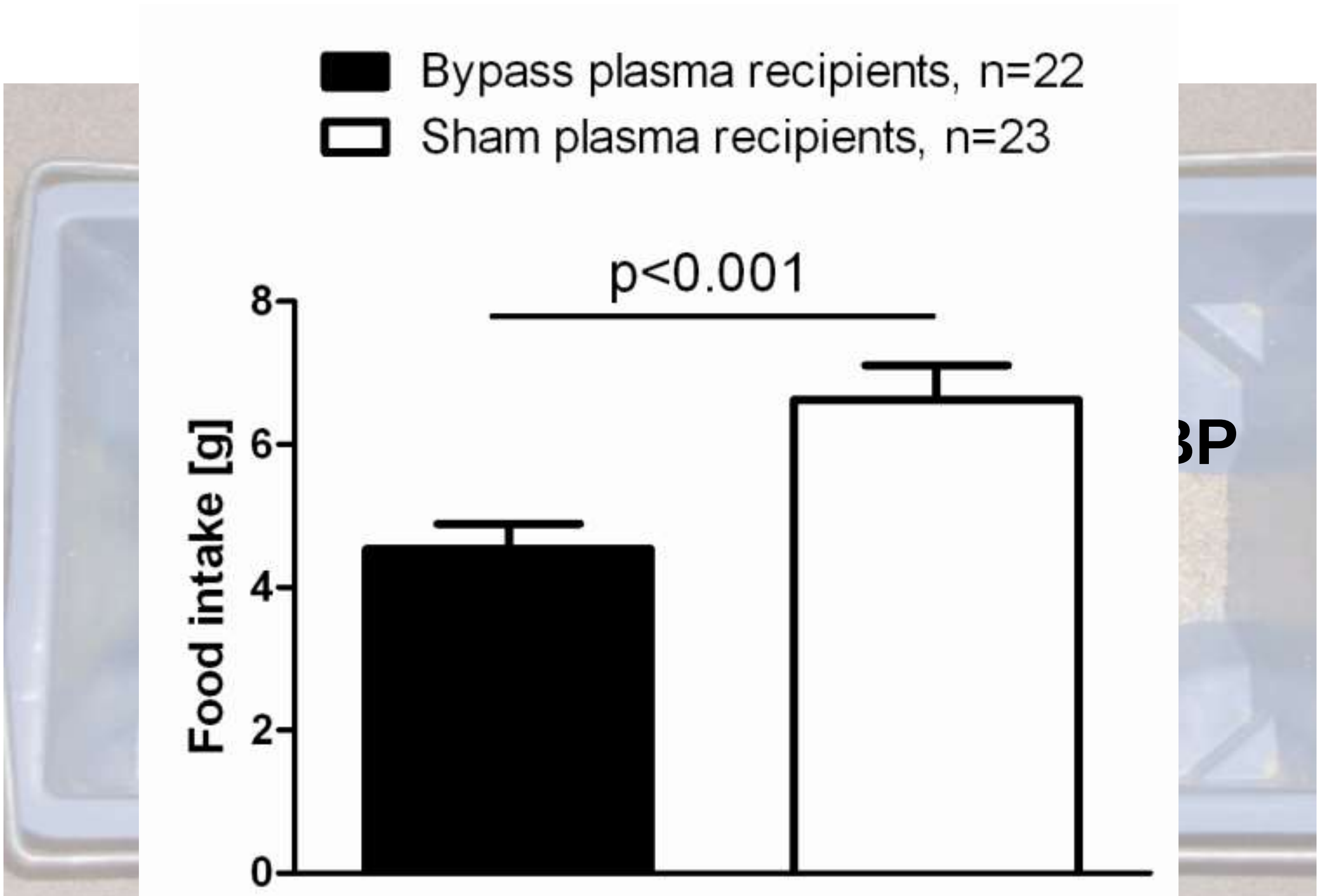
Food intake during first 24h of refeeding

Atkinson's experiment: the eating inhibitory effect of intestinal bypass depends on plasma-derived factors



Atkinson et al, Am J Physiology 243: R60-64 (1982)

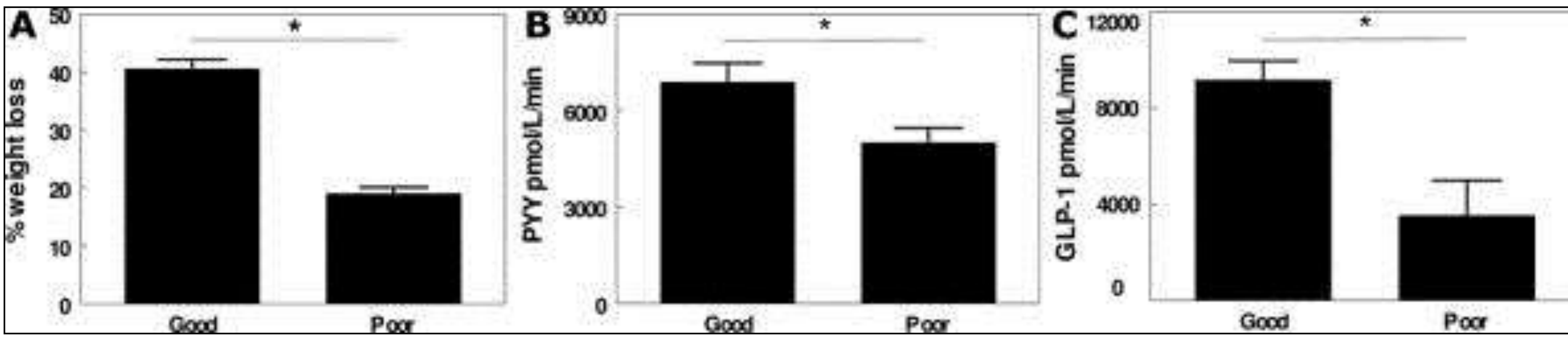
Atkinson's experiment



* no effect after administration
of plasma from fasted rats

Atkinson et al, Am J Physiology 243: R60-64 (1982)

GI hormones are changed after RYGB: PYY and GLP-1 after RYGB in humans in good versus poor responders

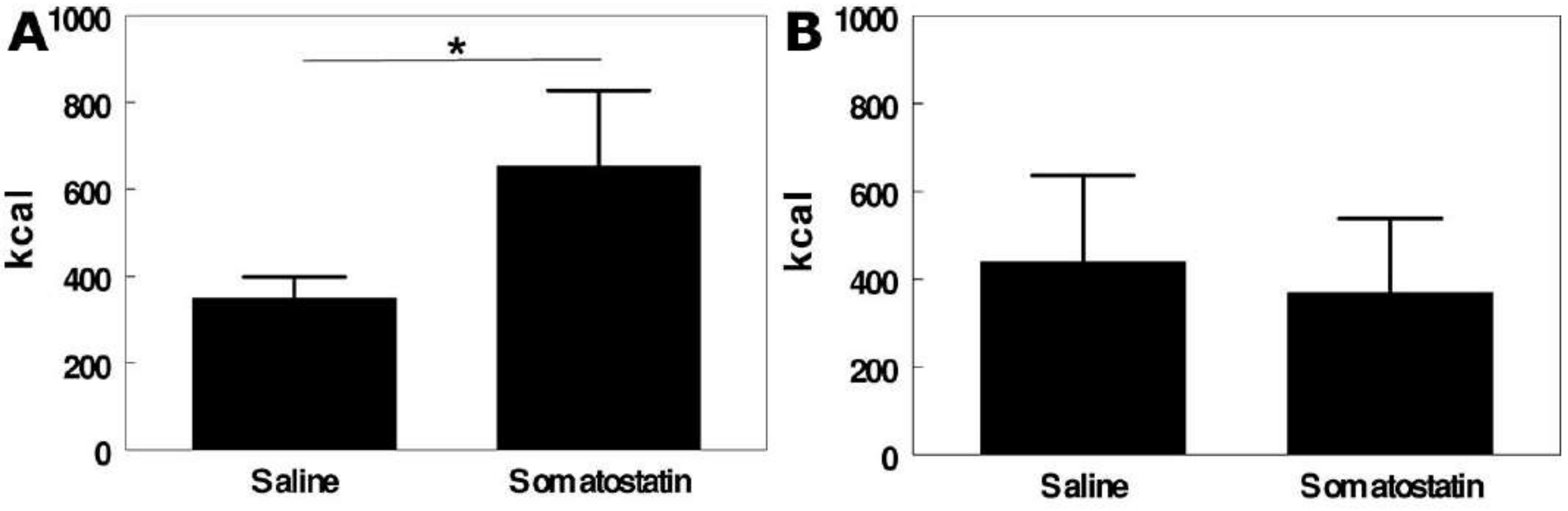


le Roux et al, Ann Surg 2007

GI hormones are changed after RYGB: Blockade of gut hormone release with Octreotide

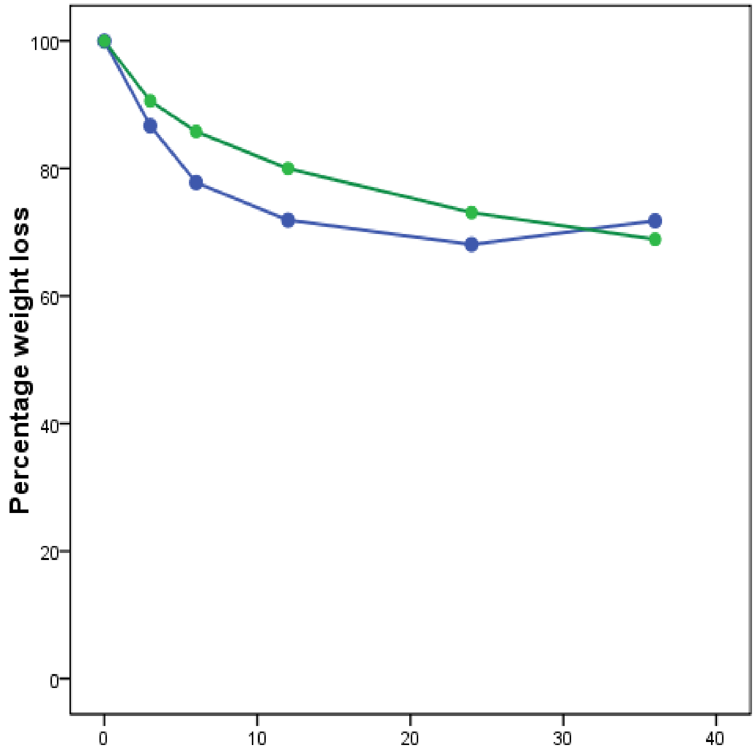
RYGB bypass

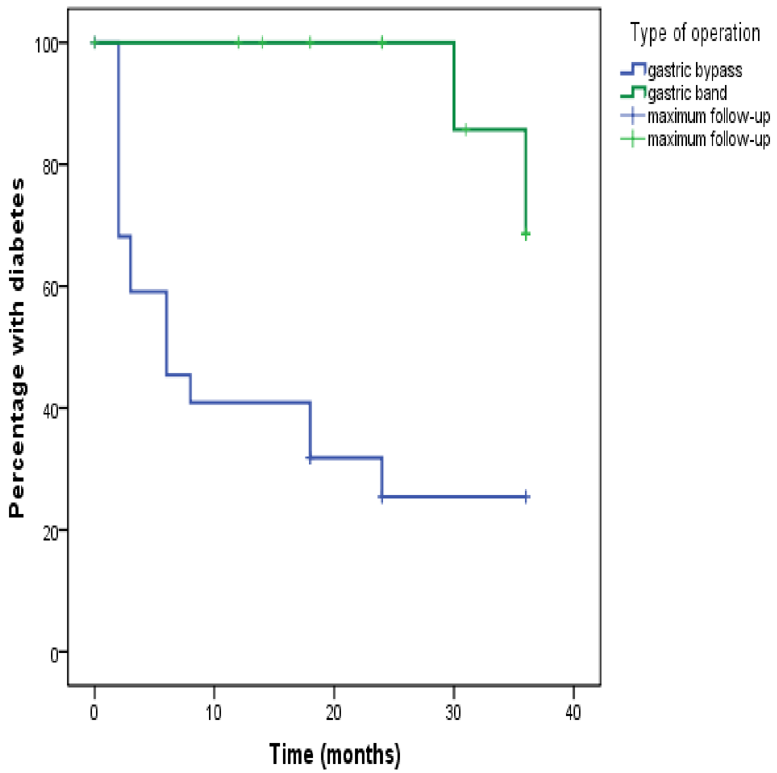
control = Gastric banding



le Roux et al, Ann Surg 2007
see also: Fenske et al, IJO 2011

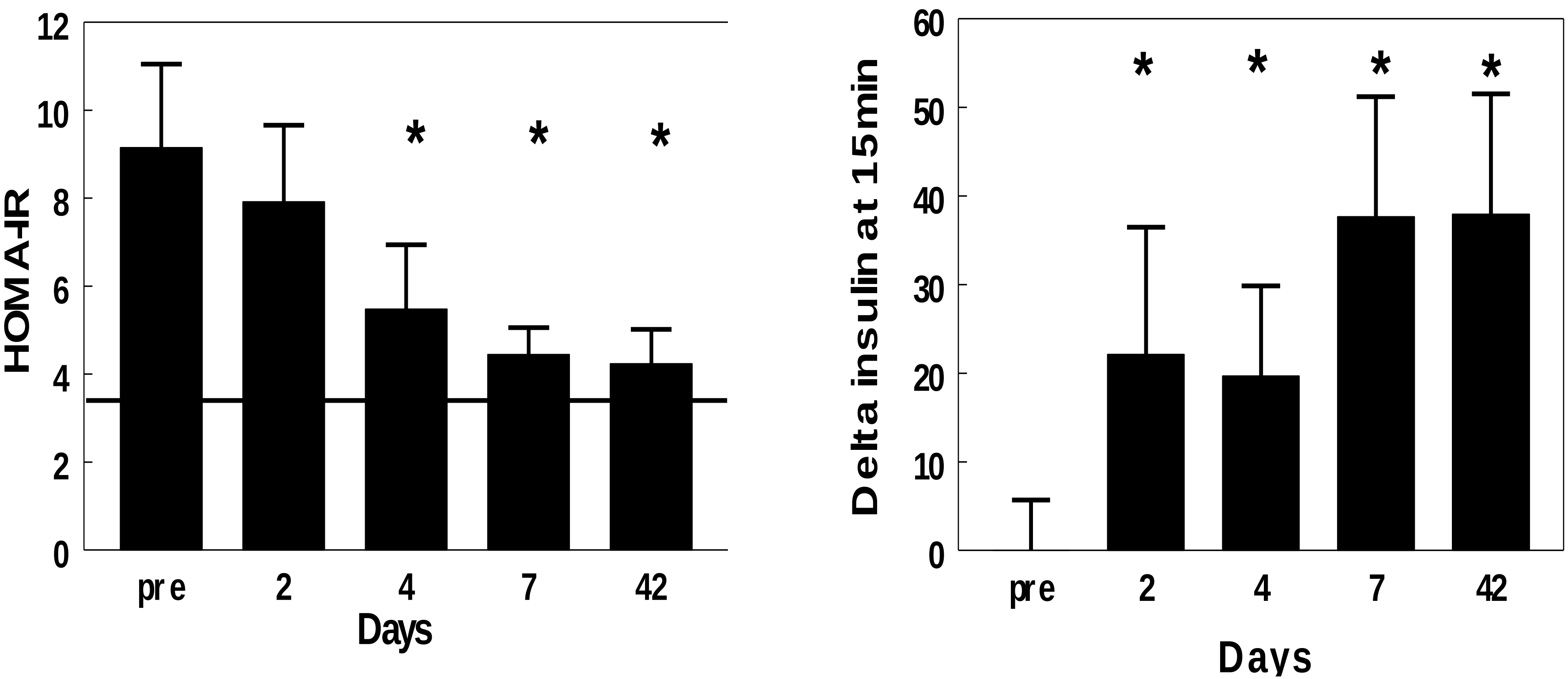
Resolution of Type 2 Diabetes





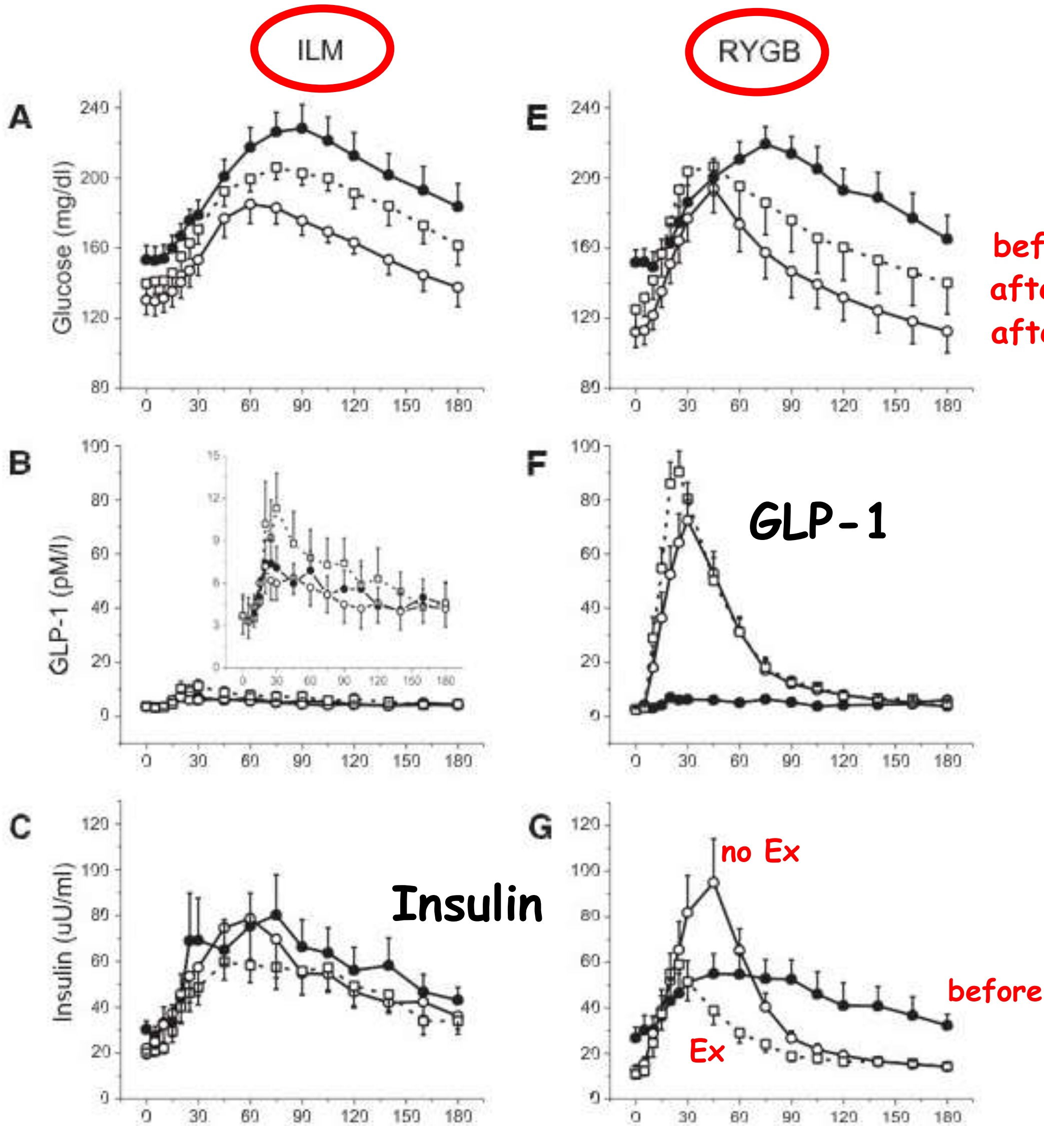
Pournaras D et al, Ann Surg 2010

Resolution of Type 2 Diabetes



Pournaras D et al, Ann Surg 2010

What is the role of GLP-1 in postprandial metabolic changes after RYGB?
RYGB versus intensive life style treatment



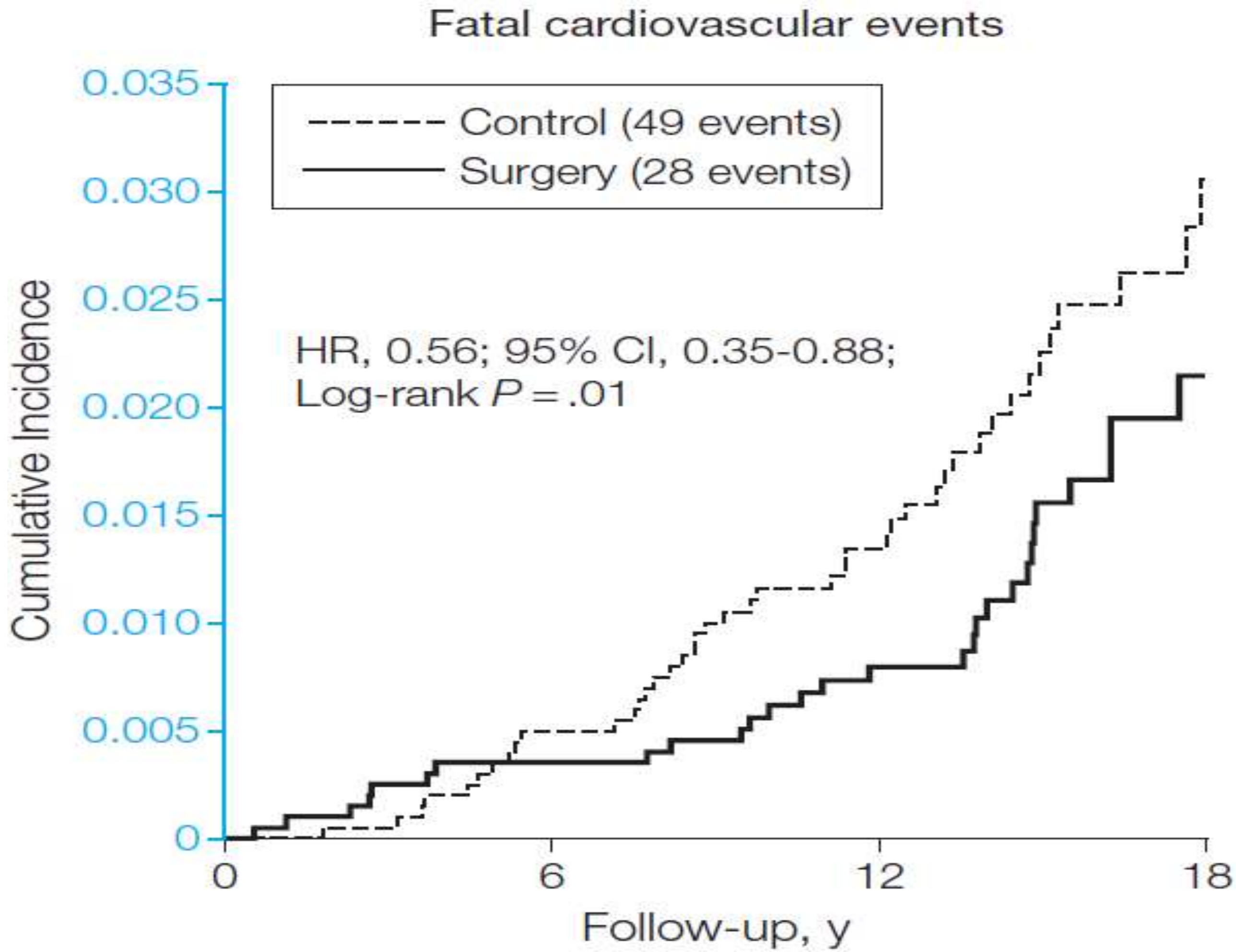
Vetter et al, 2015

Responses to liquid a meal test in RYGB patients versus Intensive Lifesytle Modification

See also
Shah et al 2014
Jimenez et al 2014
Jackness et al 2013
Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and β-cell function in type 2 diabetic patients

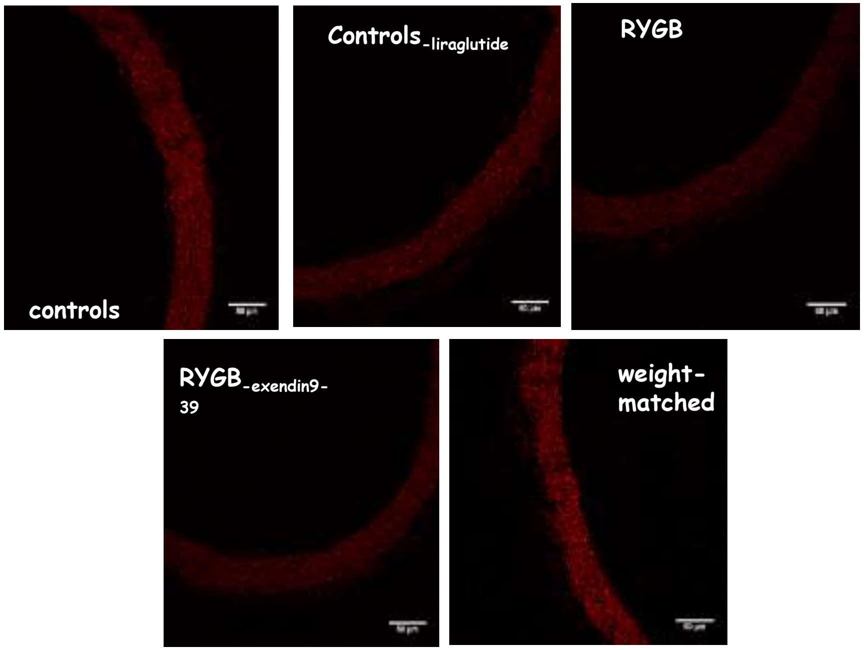
Bariatric surgery reduces cardiovascular events

Sjöström et al
JAMA 2012



RYGB improves endothelial and HDL function:

Superoxide anions



Endothelium:
-increased NO production
-reduced oxidative stress

HDL:
-increased eNOS activity
-increased NO production
-reduced VCAM expression
-improved antioxidative properties
-improved cholesterol efflux

Osto E et al. Circulation 2015

Correction of periprandial hyper- and hypoglycemia is clinically relevant

- Disruptions in glucose homeostasis can continue even years after RYGB and can lead to relapse of diabetes.
- Patients undergoing RYGB spent significantly more time in hyper- and hypoglycemic states than those undergoing sleeve gastrectomy

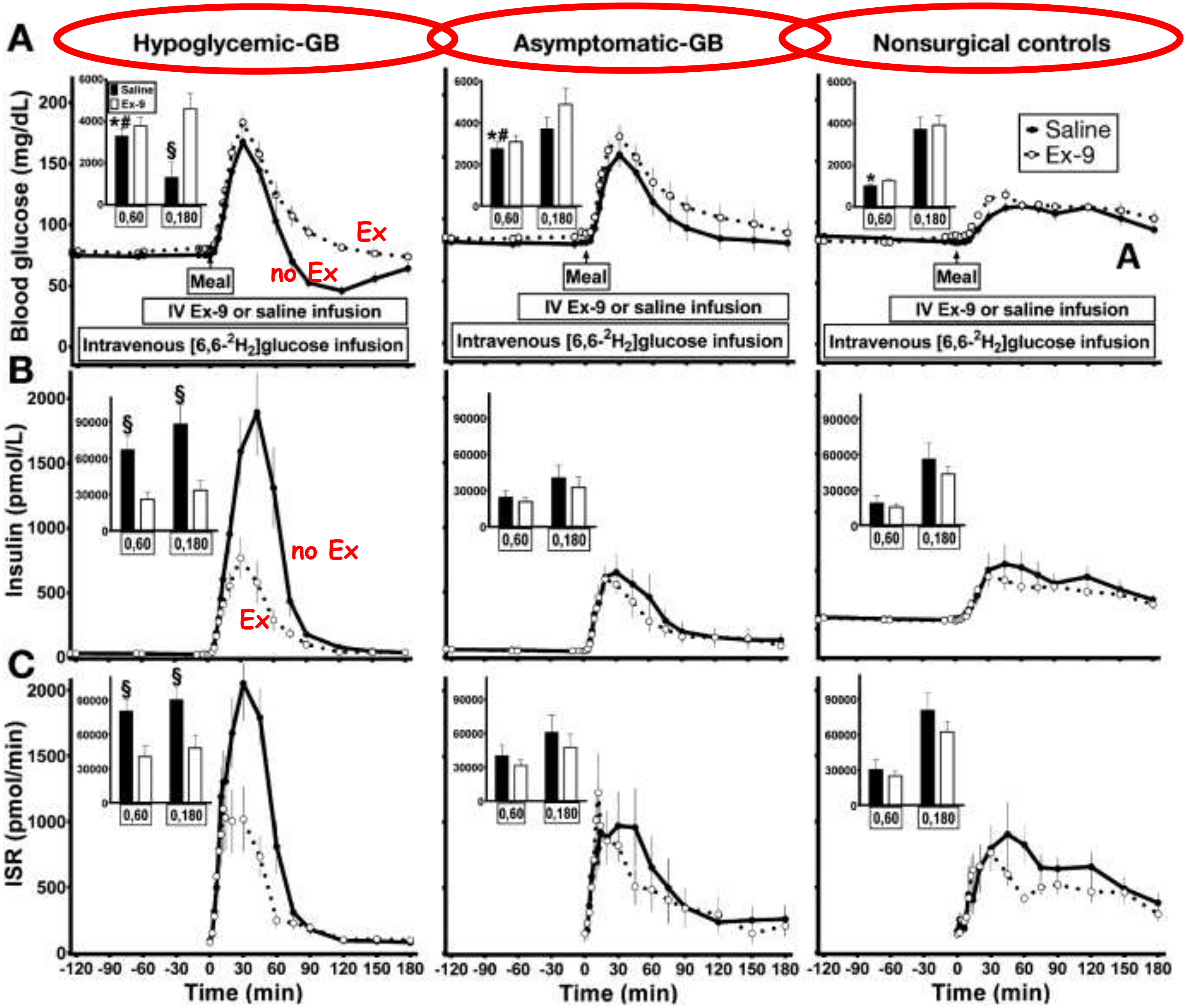
TABLE 2. Clinical Characteristics and Data From Continuous Glucose Monitoring in Subjects in Remission of T2DM After Roux-en-Y RYGBP or SG

	RYGBP (n = 8)	SG (n = 8)	*P*
Gender, M/F	1/7	3/5	0.248
Age, yr	49.2 ± 13.0	47.2 ± 6.8	0.707
Duration of T2DM before surgery, median (IQR), yr	3 (1.2–5.5)	2.5 (1.0–8.7)	0.750
Time of postsurgical follow-up, yr	2.8 ± 1.5	2.5 ± 0.6	0.622
BMI at evaluation, Kg/m^2	28.5 ± 2.7	30.4 ± 7.7	0.522
HbA1c at evaluation, %	5.5 ± 0.5	5.6 ± 0.4	0.781
Average IG, mg/dL	98.7 ± 8.0	97.7 ± 8.8	0.816
Minimum IG, mg/dL	53.1 ± 12.1	66.4 ± 12.0	0.045
SD, mg/dL	30.6 ± 10.4	15.1 ± 4.2	0.003
Maximum IG, mg/dL	229.6 ± 41.8	153.7 ± 22.4	<0.001
Time in hyperglycemia, % **> 160 mg/dL**	4.6 ± 3.3	0.4 ± 1.1	0.009
Time in hypoglycemia, % **< 70 mg/dL**	12.7 ± 8.6	3.2 ± 4.1	0.019
Time in euglycemia, %	82.6 ± 11.0	96.4 ± 4.0	0.007

SD indicates standard deviation.

Jiménez et al, 2014

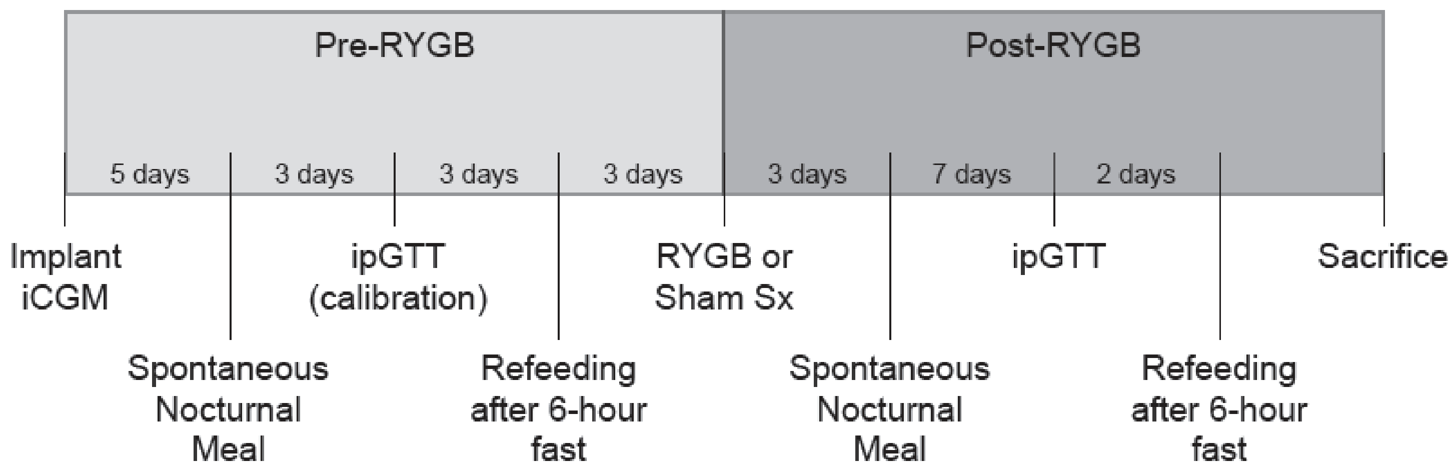
GLP-1 may play a role in the exaggerated postprandial glucose excursions after RYGB



Salehi et al, 2014

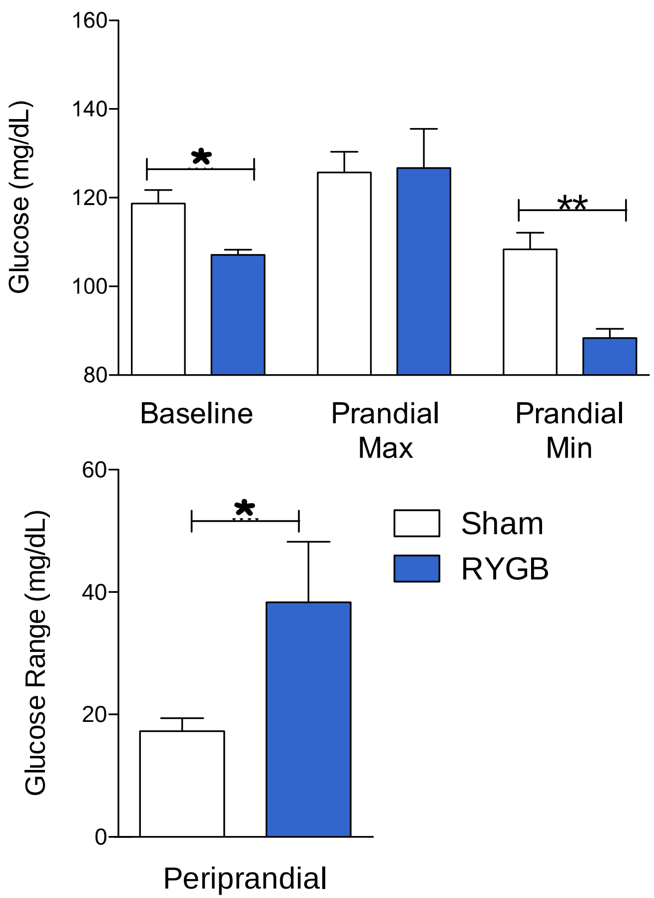
Does RYGB alter meal-induced glucose excursions in rats?

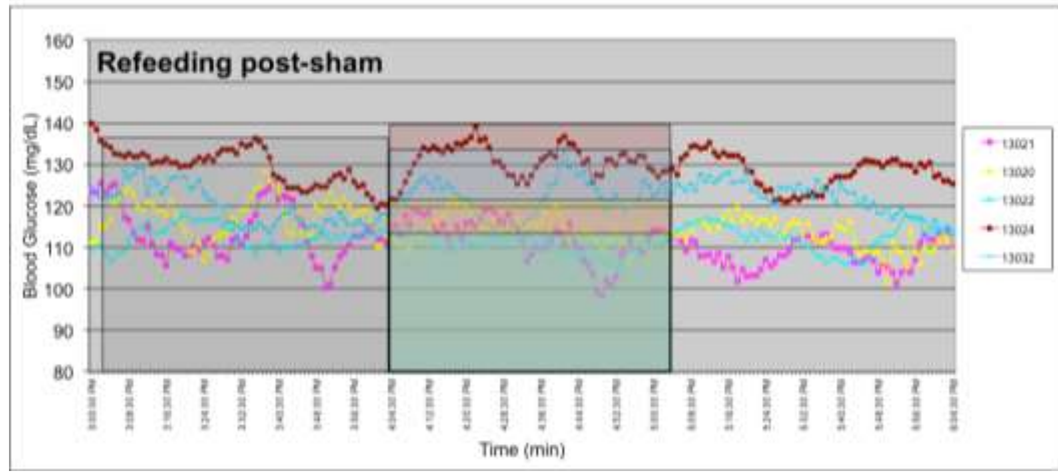
- 12 male Sprague Dawley rats (450-550 g)
- Housed in cages equipped with BioDAQ food intake monitoring system
- Rats maintained on standard chow
- Intravascular glucose telemetry sensor (DSI) transmitted glucose data every 30-60s

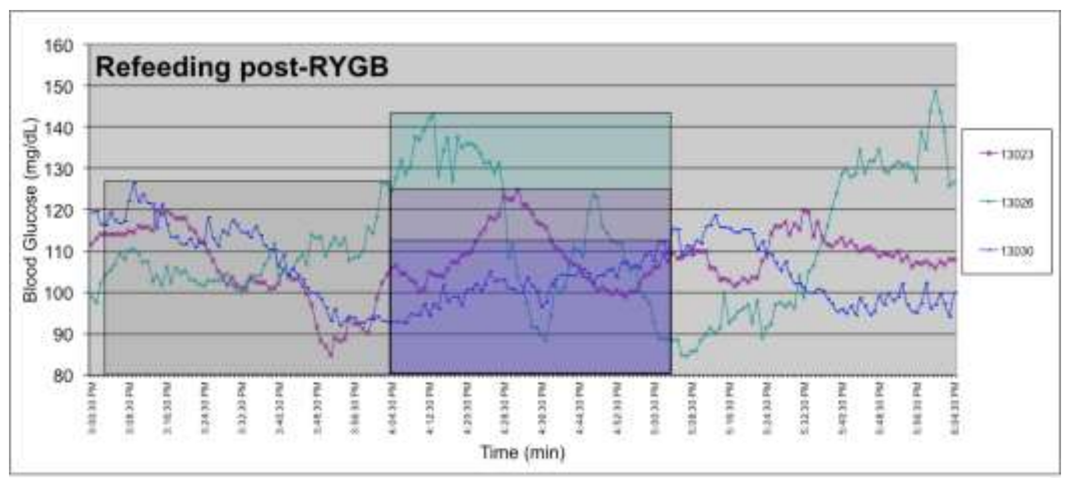


RYGB increases prandial glucose excursions: Refeeding after 6-hour fast

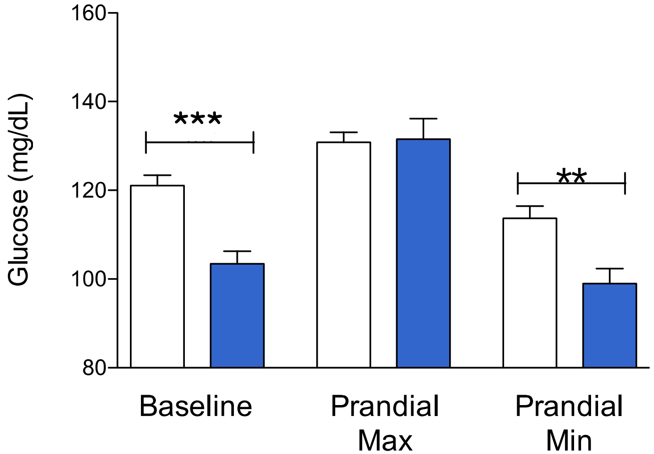
Periprandial Analysis Parameters (1-h post-meal initiation)

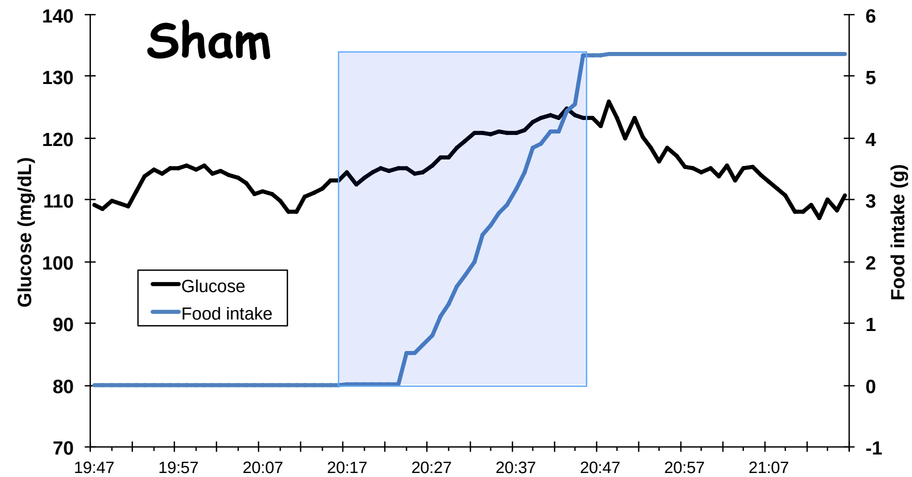


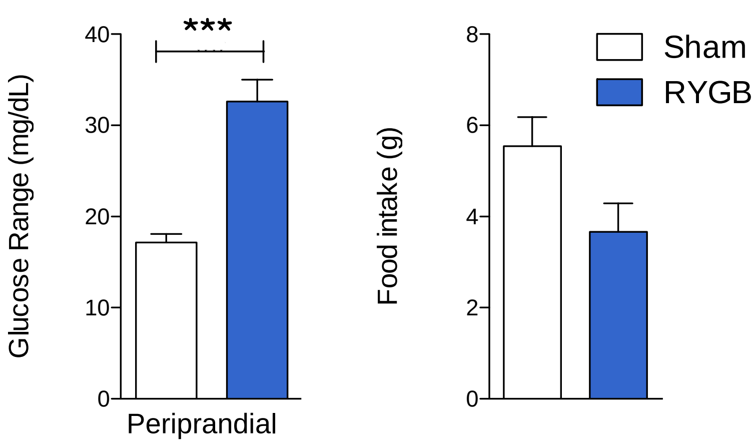


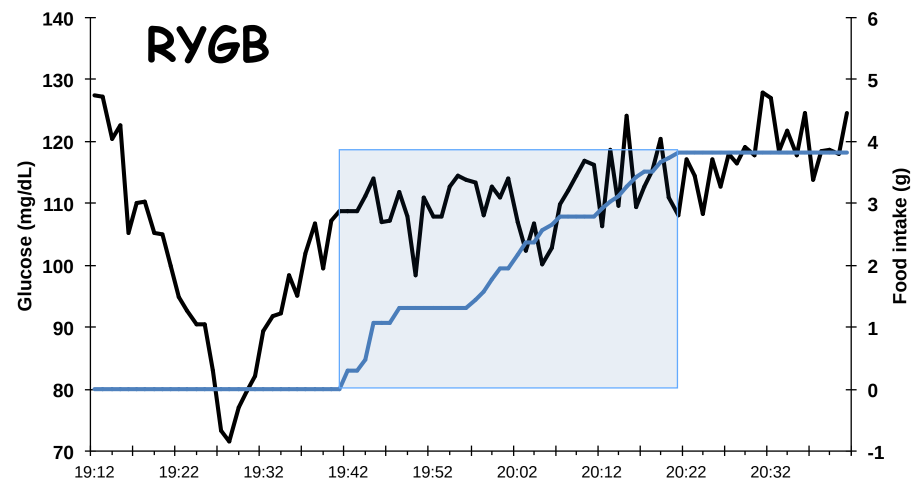


RYGB increases prandial glucose excursions: Spontaneous nocturnal meals

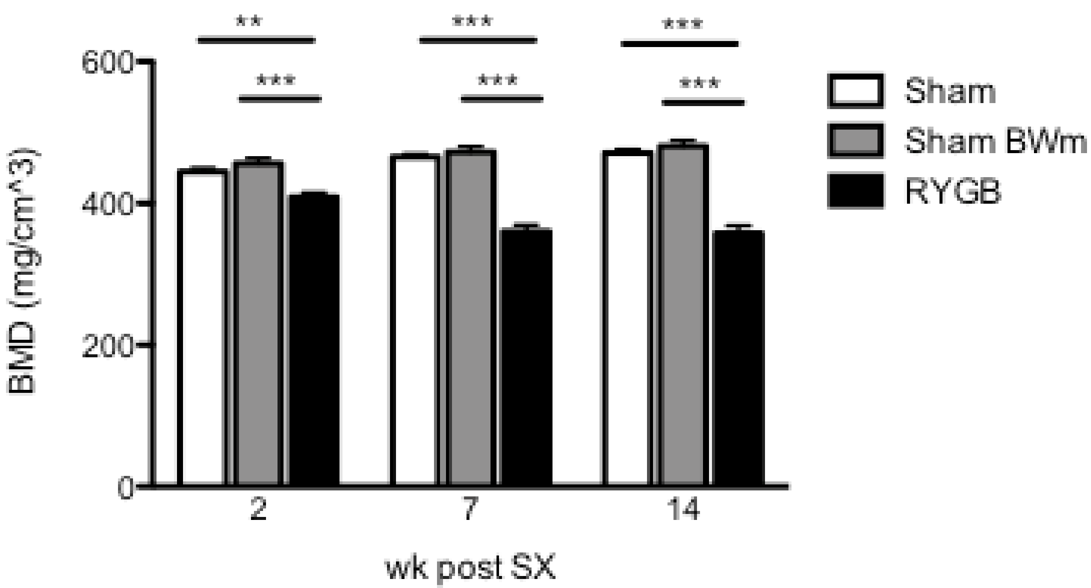




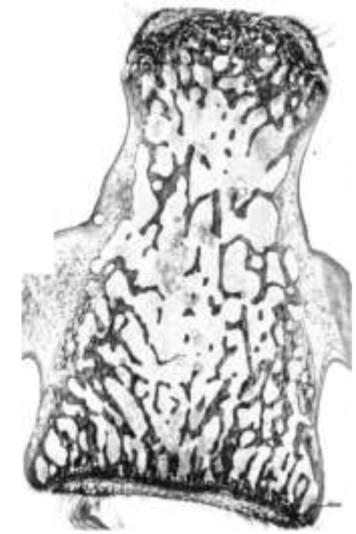




Bone mineral density (BMD) decreases rapidly post RYGB

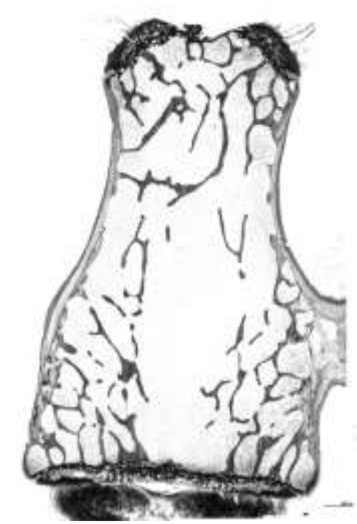


SHAM



SHAM BWM

RYGB



Mechanisms:

- Temporary reduction in Ca absorption
- Increased (sustained) renal Ca losses
- Reduced 25-Vit D
- Massive increase in 1,25-Vit D
- Metabolic (lactic) acidosis

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