Praliciguat, a clinical-stage sGC stimulator, improved insulin sensitivity, lipid tolerance and energy utilization in a diet-induced obesity mouse model

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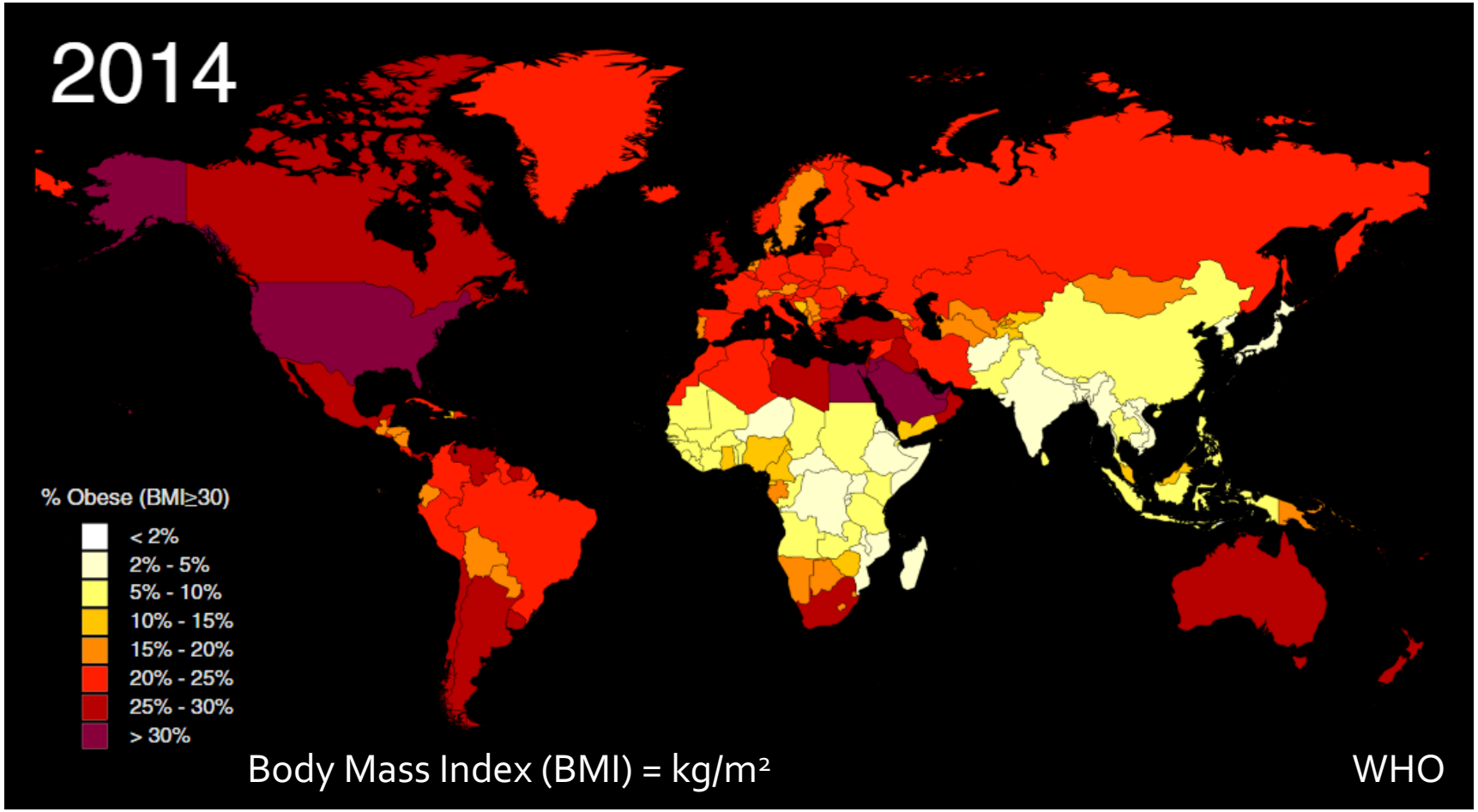
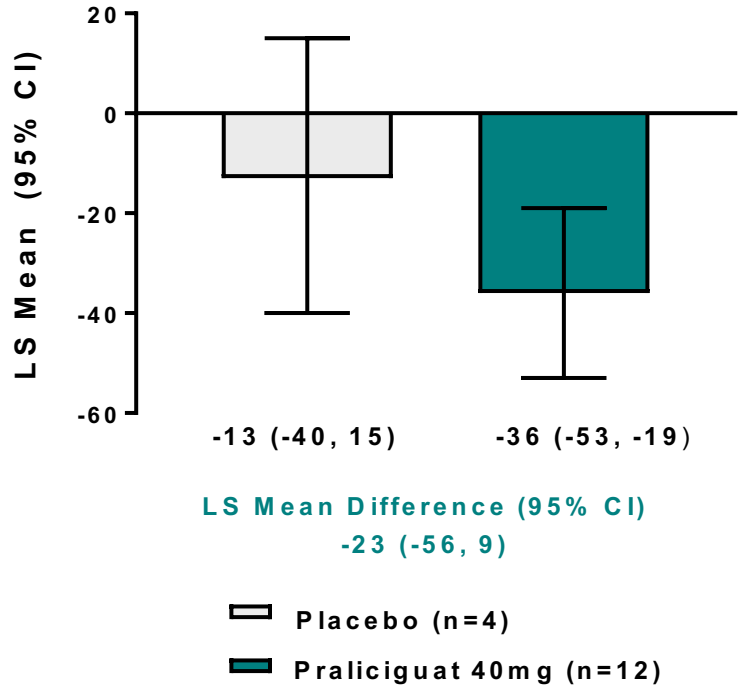
The current prevalence of obesity is alarming



- In 2014, an estimated 900 million worldwide were obese and 1.5 billion were overweight
- Obesity is associated with numerous comorbid conditions such as diabetes, cardiovascular disease and cancer

Clinical experience with the sGC stimulator praliciguat suggests potential metabolic benefit

Change in HOMA-IR (%)
patients not on concomitant insulin therapy

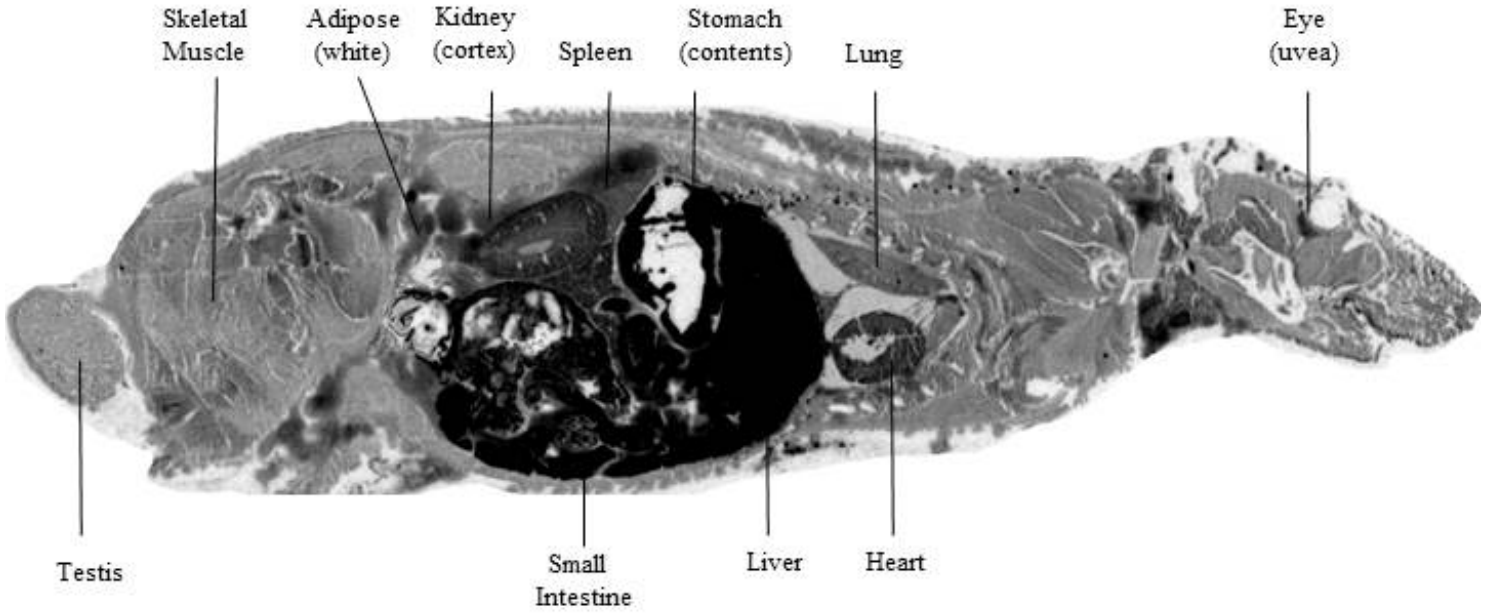


NCT03091920

- Praliciguat (IW-1973) is currently in Phase 2 for diabetic nephropathy and HFpEF
- In an exploratory Phase 2 study in 26 patients with type 2 diabetes and hypertension on standard of care therapy, 14 days of praliciguat treatment showed positive trends in reducing
  - Fasting plasma glucose
  - HOMA-IR
  - LDL cholesterol
  - Triglycerides

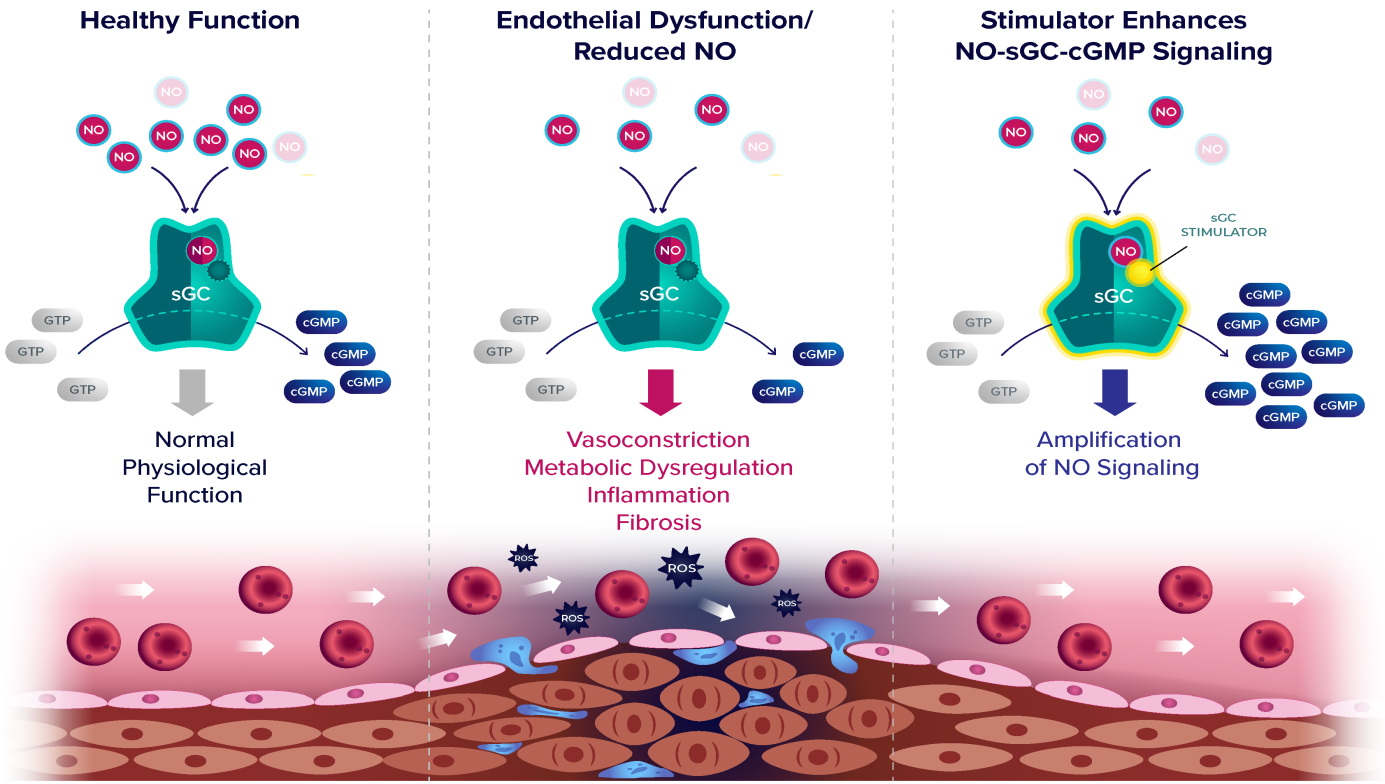
➢ **The purpose of the current studies was to explore the mechanism of action behind the potential metabolic benefits of praliciguat utilizing an obese mouse model**

Praliciguat shows extensive distribution to key target tissues



	Heart	Liver	Kidney	Lung	Skeletal Muscle	Adipose
Tissue/plasma C_{max} ratio	5.0	53.0	9.6	4.1	3.1	12.5

Enhanced NO-sGC-cGMP signaling by praliciguat demonstrates benefits in preclinical models



- In preclinical models, compared to disease controls, animals treated with praliciguat have:
  - Preserved cardiac function
  - Less cardiac hypertrophy
  - Lowered biomarkers of inflammation and fibrosis
  - Less renal damage

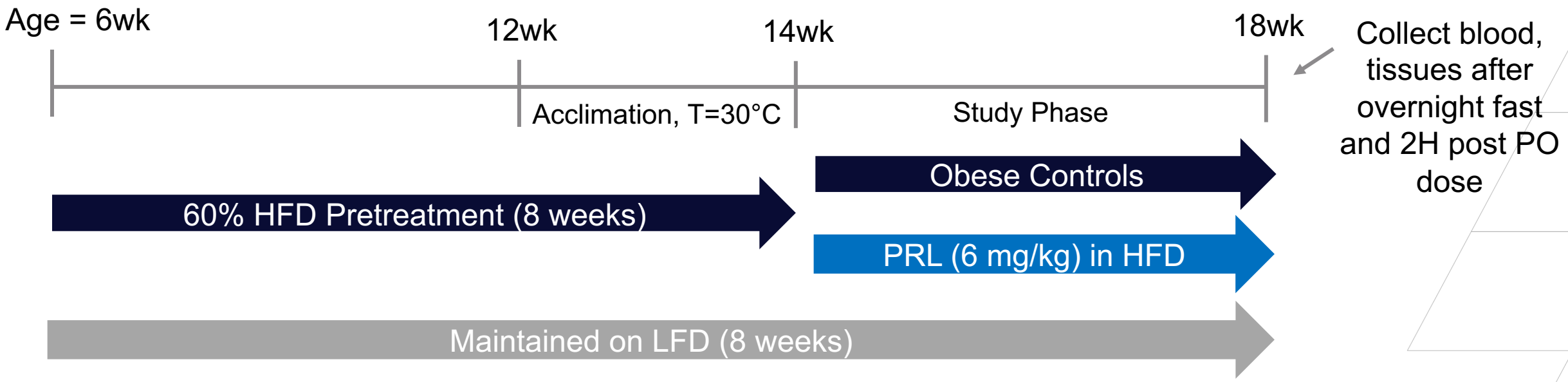
Adapted from Tobin, Zimmer et al. J Pharmacol Exp Ther 2018;365:664-675. Copyright © 2018 The Author(s).

Diet-induced obesity (DIO) mouse model is a common preclinical model of insulin resistance

- Simple model: C57Bl/6 mice are switched to 60% high fat diet (HFD) at 6 weeks of age
- Within 3 weeks mice develop an obese phenotype
  - Increased adiposity
  - Insulin resistance
  - Leptin resistance

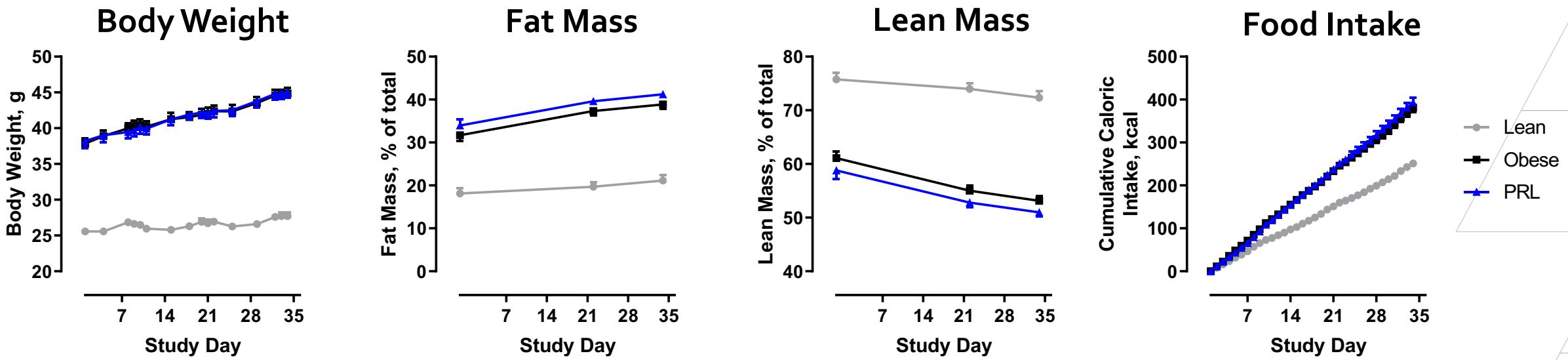
- HFD is continued throughout study and animals will continue to gain weight
- Widely used in anti-obesity and metabolic syndrome research
  - Animals will lose weight on anorectic drugs (GLP-1, phentermine)
  - Animals will increase insulin sensitivity/secretion when on anti-diabetic drugs (GLP-1, metformin, rosiglitazone)

Study Design



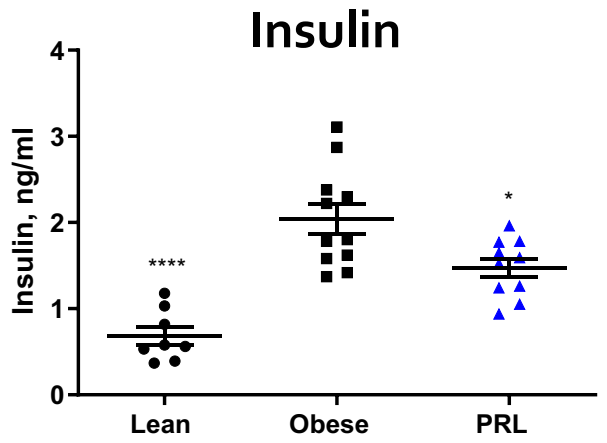
- **Study was performed at thermoneutrality (30° C)**
  - **Housing animals below their thermoneutral zone alters energy expenditure and substrate utilization**
  - **Cold stress undermines mouse modeling (Karp, J. Exp. Med. Vol. 209 No. 6 1069-1074 (2012))**

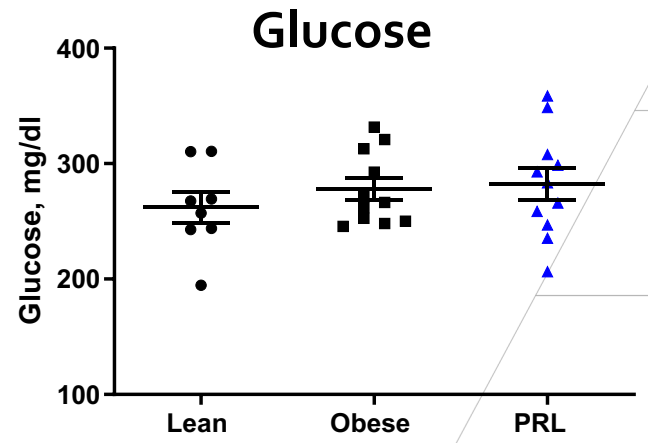
Praliciguat did not alter body weight, food intake or body composition

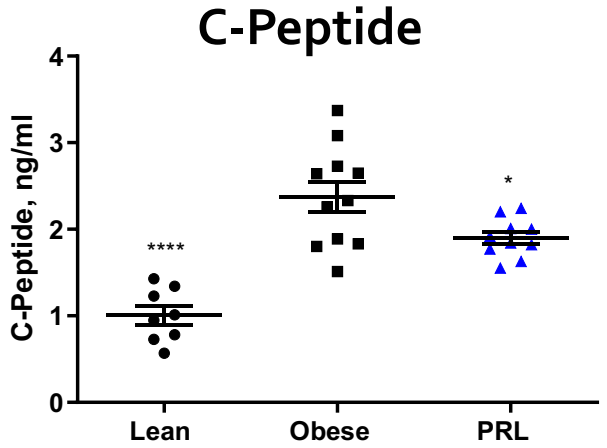


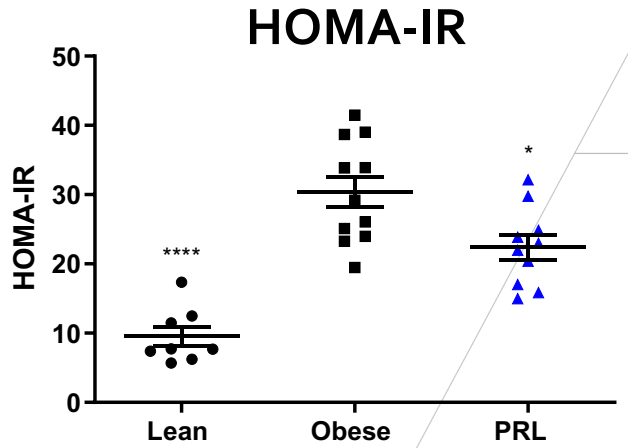
Praliciguat-treated mice had greater insulin sensitivity than control DIO mice

- Compared to obese mice, four weeks of praliciguat resulted in:
  - Lower fasting insulin
  - Lower C-peptide
  - Lower HOMA-IR
- In this model, fasting glucose was not altered in obese or PRL-treated mice

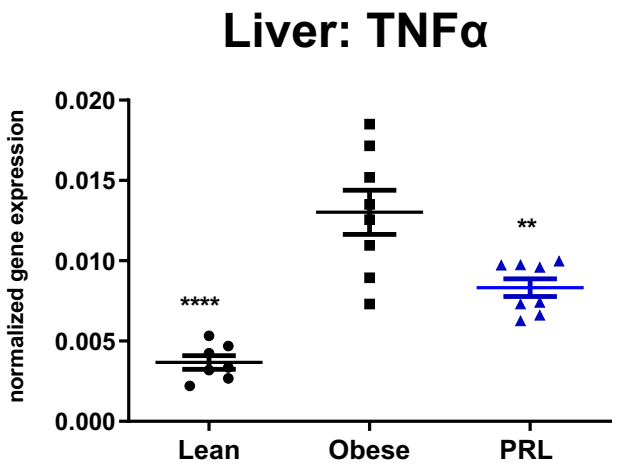


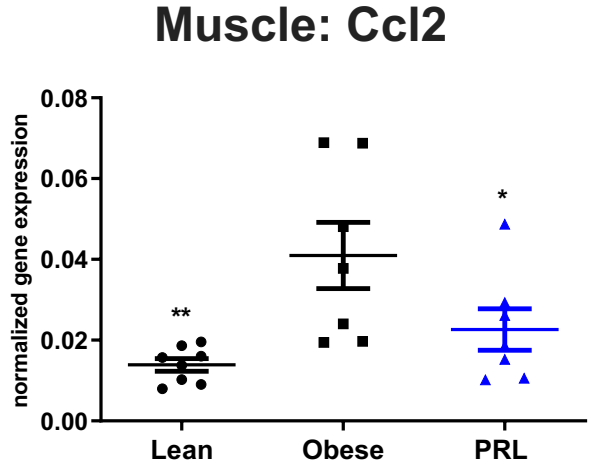


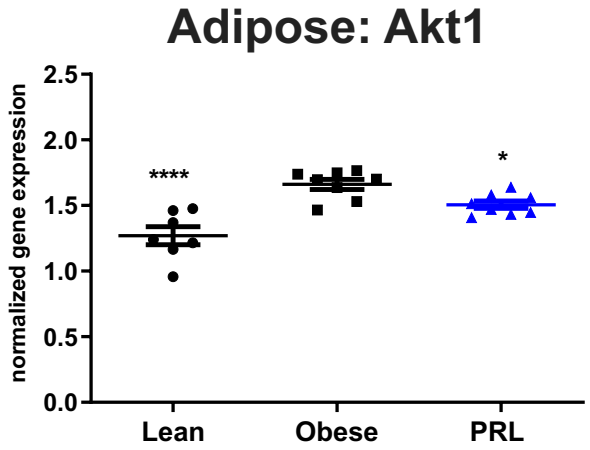


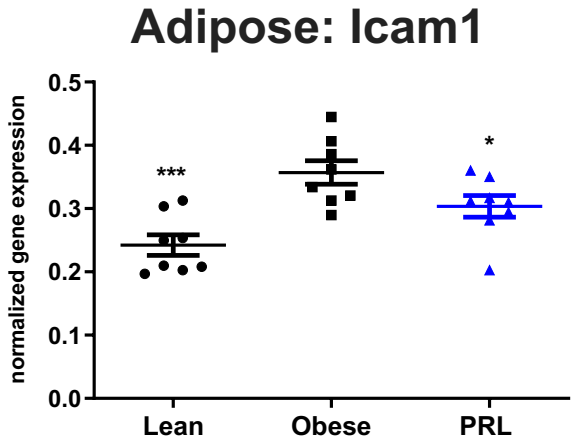


DIO mice treated with praliciguat had lower expression of genes involved in inflammation



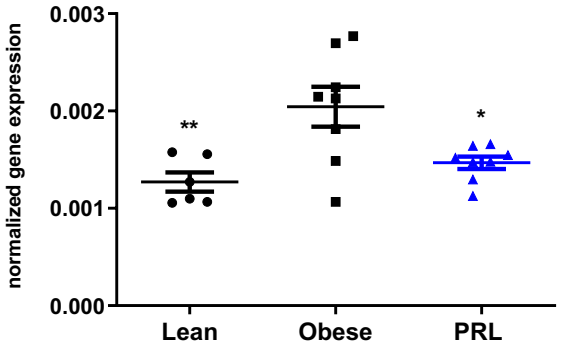




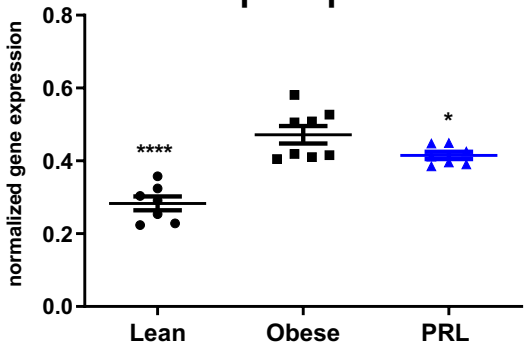


DIO mice treated with praliciguat had normalized expression of genes involved in lipid handling

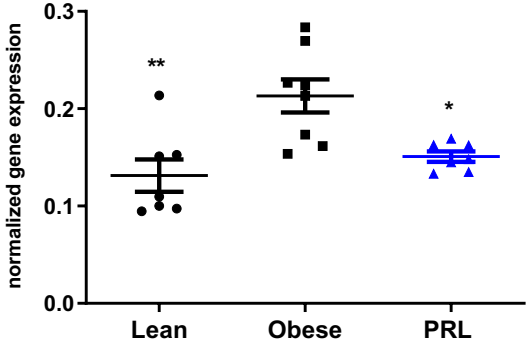
Liver: Pnpla3



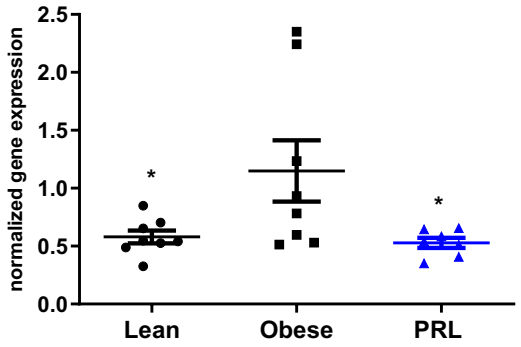
Liver: Long-chain fatty acid transport protein 1



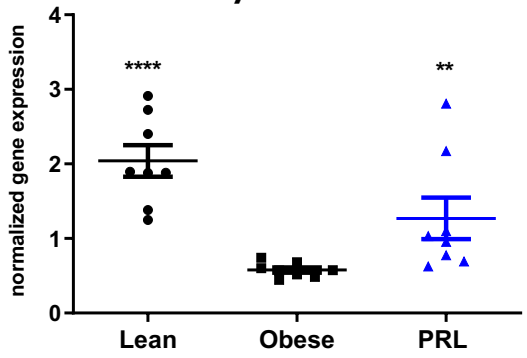
Liver: Lipoprotein lipase



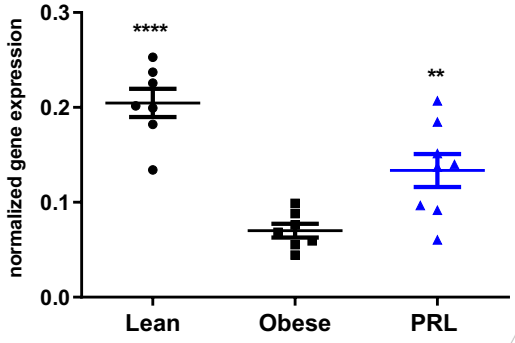
Muscle: Hormone-sensitive lipase



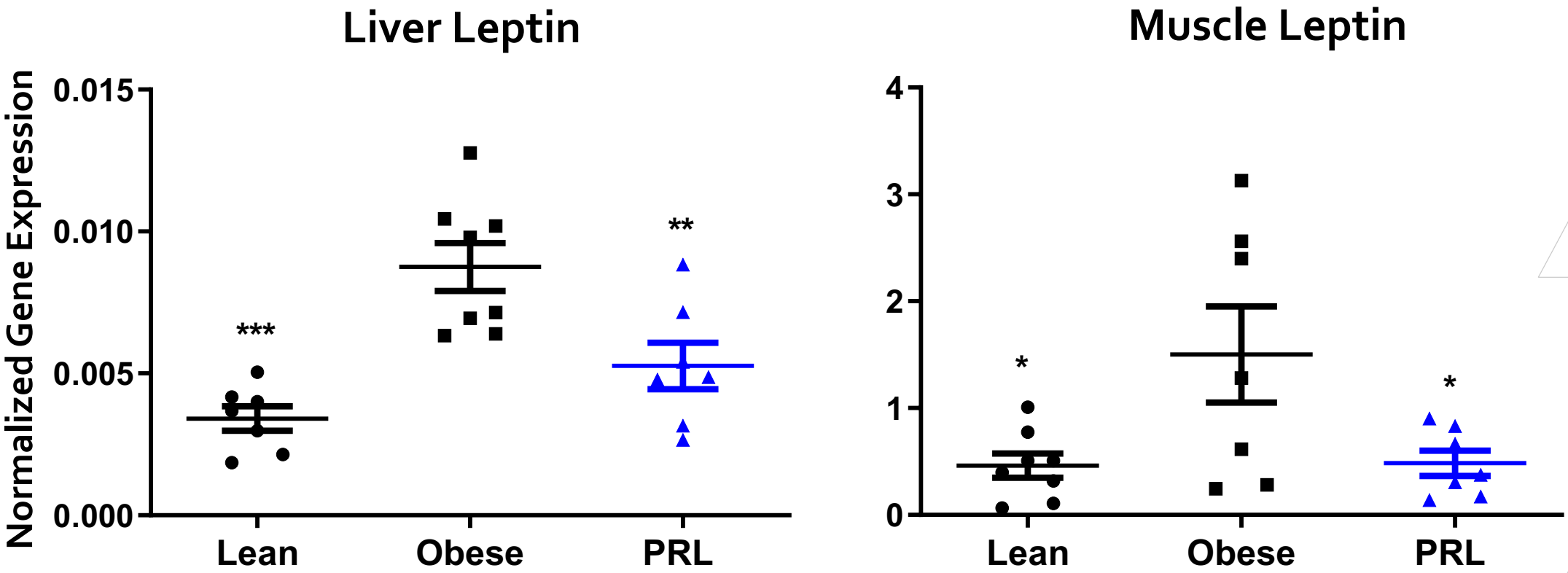
Adipose: Farnesyl-diphosphate farnesyltransferase 1



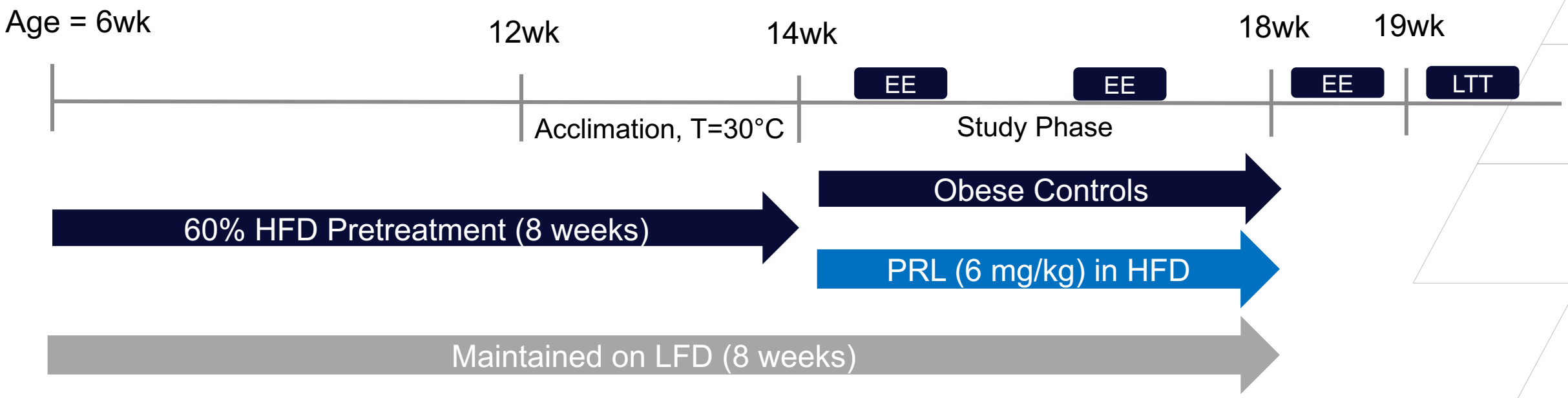
Adipose: Pparα



DIO mice treated with praliciguat had lower expression of leptin in liver and muscle suggesting repartitioning of adipose tissue

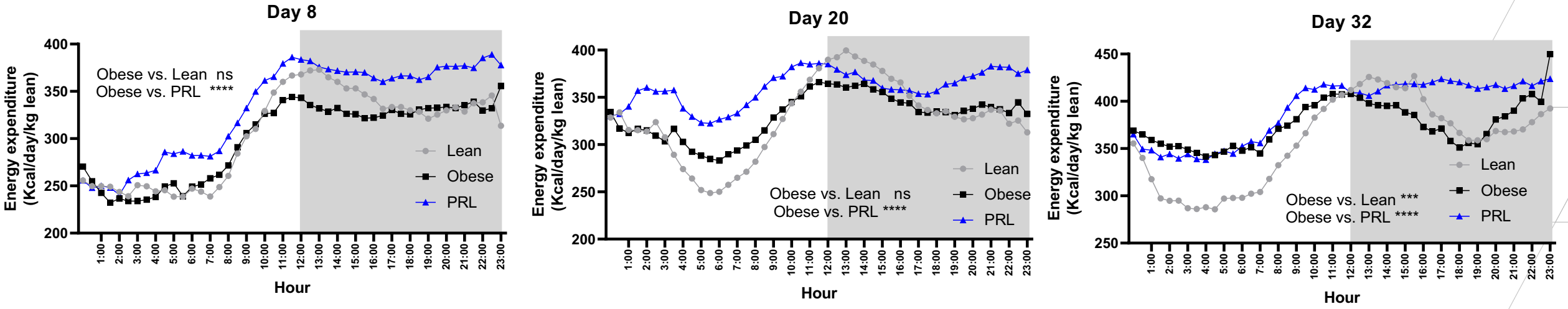


The assessment of praliciguat on energy expenditure and lipid handling



- **Energy expenditure (EE) was measured on day 8, 9, 20, 21, 32 and 33**
- **A lipid tolerance test (LTT) was performed on day 38**

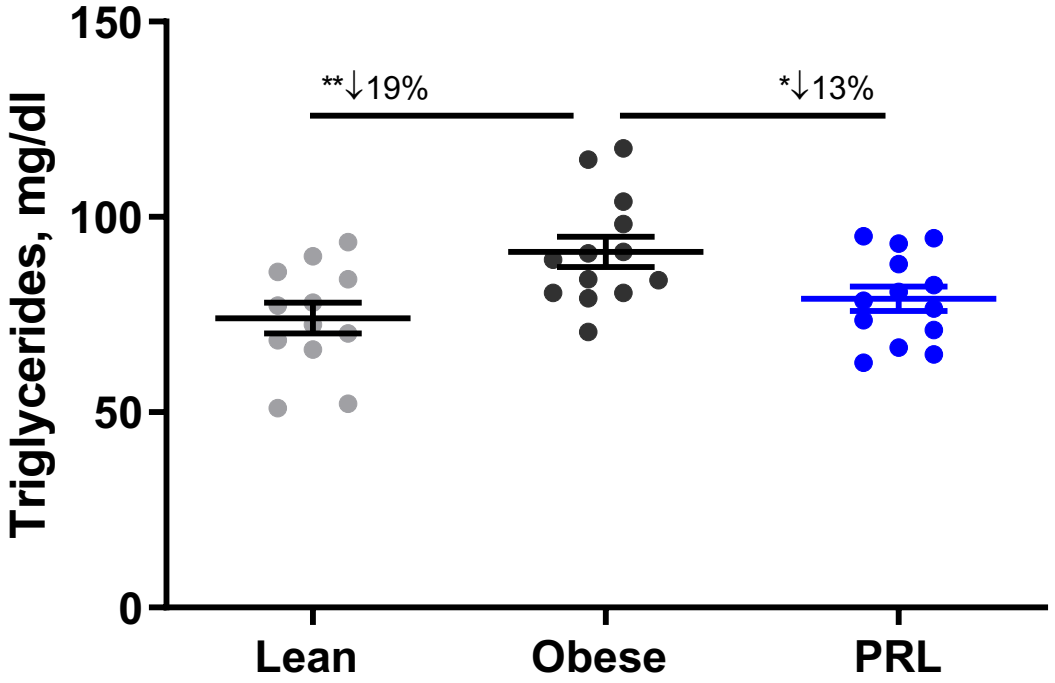
Praliciguat-treated mice had a mild increase in energy expenditure compared to obese controls



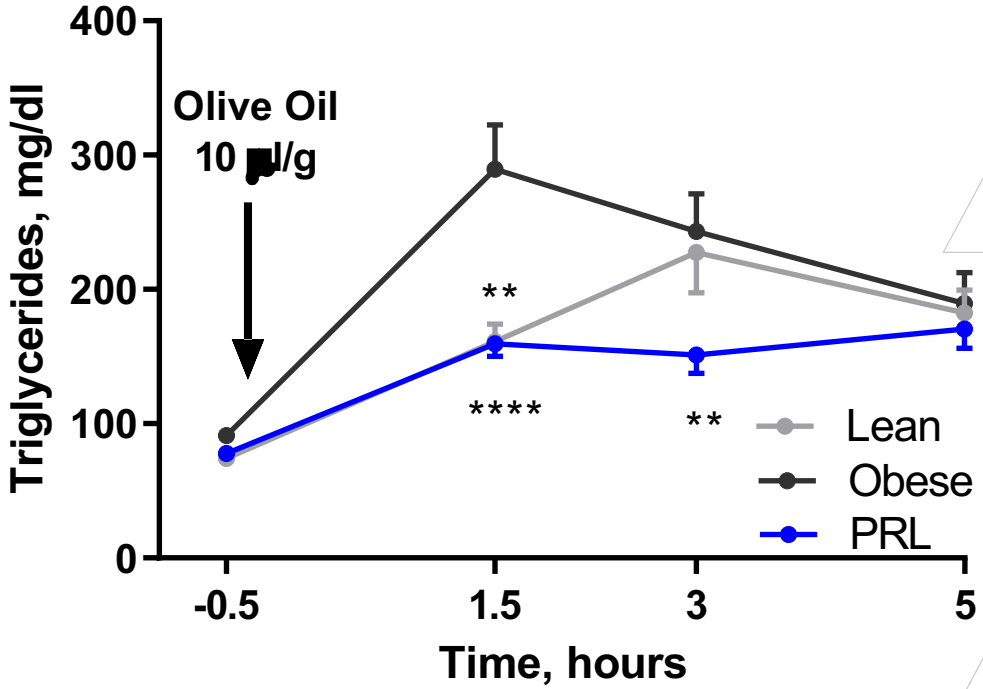
- Increase in energy expenditure was accompanied with an increase in fat oxidation through day 21.

DIO mice treated with praliciguat had lower plasma triglycerides content suggesting improved lipid handling

Fasting Plasma Triglycerides

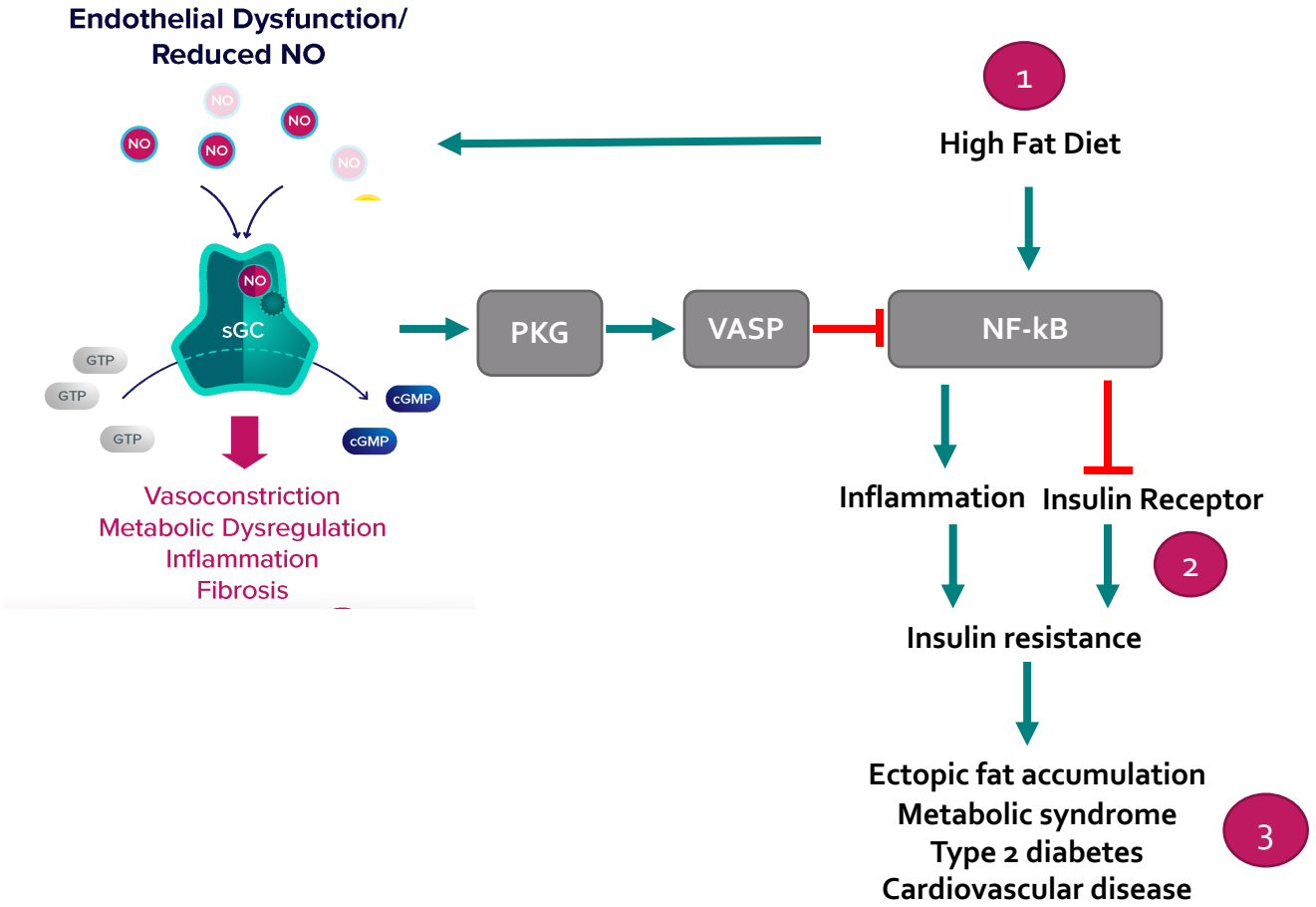


Oral Lipid Tolerance Test



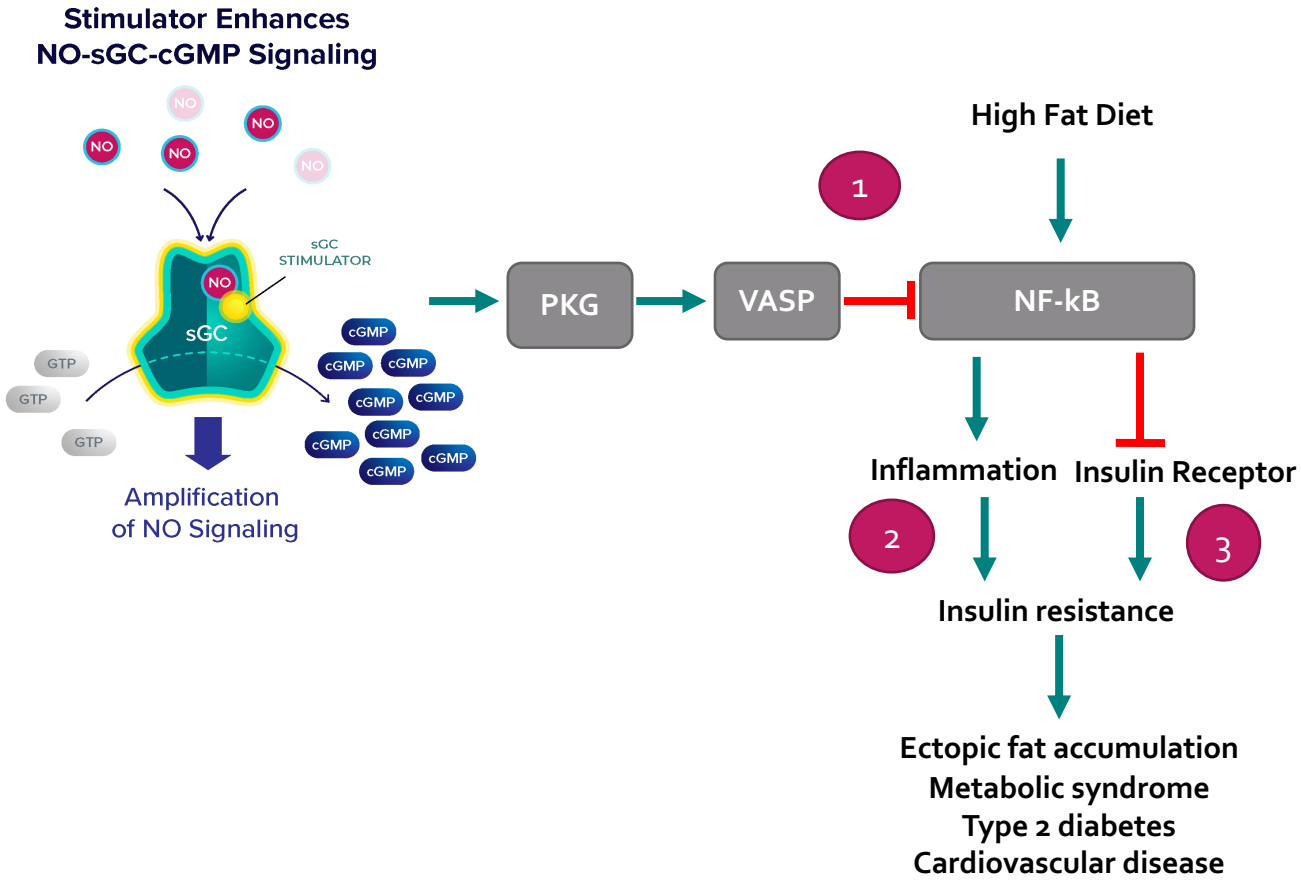
Inflammation and NO insufficiency impair insulin signaling

1. The consumption of high-fat diet can lead to obesity resulting in reduced NO signaling
2. Reductions in VASP and high fat diet both increase NF-kB, which increases inflammation and inhibits insulin signaling leading to insulin resistance
3. All of these factors lead to comorbid metabolic conditions

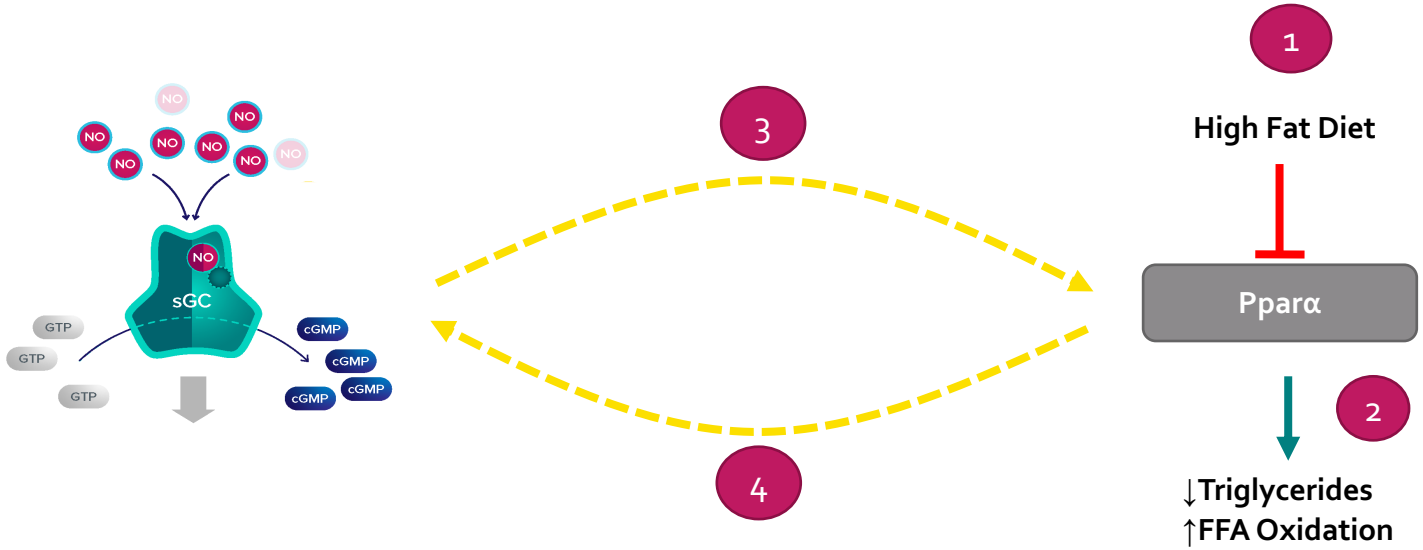


Praliciguat's effect on inflammation and insulin sensitivity in DIO mice may be due to inhibition of NF-kB activation

1. NO-sGC-cGMP signaling stimulates VASP phosphorylation which inhibits NF-kB
2. Praliciguat-treated mice had lower levels of inflammatory gene expression across target tissues
3. The increased insulin sensitivity in praliciguat-treated mice may be due to its effects on the NF-kB signaling pathway



Improved lipid handling in praliciguat-treated DIO mice may be in part due to the increase in adipose Pparα



1. High fat diet inhibits Pparα; yet praliciguat-treated mice had a restoration in adipose tissue pparα gene expression
2. Pparα decreases triglycerides and increases FFA oxidation
3. Dietary nitrate enhance Pparα and Pparβ/δ activity
4. Pparα agonists such as fenofibrate have been demonstrated to increase NO via eNOS

Summary

- The positive trends in several metabolic parameters observed in humans following praliciguat treatment is recapitulated in DIO mice including reduced fasting insulin, HOMA-IR, and fasting triglycerides
- Praliciguat did not affect plasma glucose, body weight, food intake or body composition
- Praliciguat treated-mice had positive changes in the expression of genes associated with inflammation and lipid metabolism in key metabolic tissues
- The effects of praliciguat on inflammation and insulin sensitivity may be explained by inhibition of NF-kB signaling
- The effects of praliciguat on lipid handling may be mediated by activation of Pparα
- These data demonstrate broad metabolic effects such as improved insulin sensitivity, lipid handling and increased energy utilization in obese mice housed at thermoneutrality

Questions?