PXL770, a novel direct AMPK activator, improves metabolic disorders in a diet-induced mice model of obesity and diabetes

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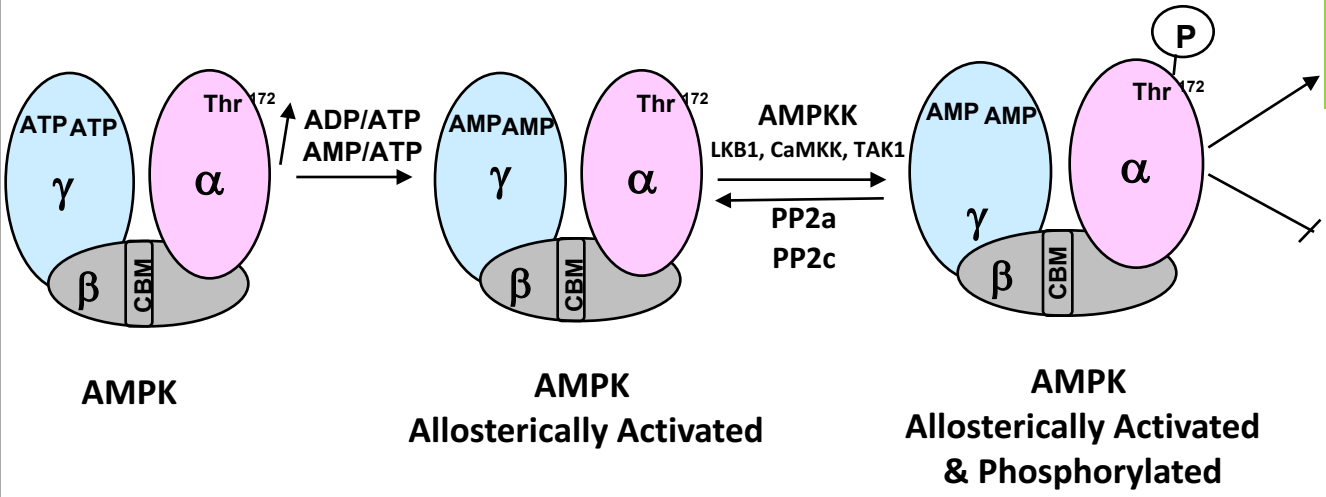
Presenter Disclosure Information

- Sébastien Bolze, Pharm D, PhD, is an employee of Poxel SA

Why Activating AMP Kinase is of Interest for the Management of Metabolic Disorders?



Glucose Uptake
Glycolysis
Fatty Acid Uptake
Fatty Acid Oxidation
Mitochondria Biogenesis

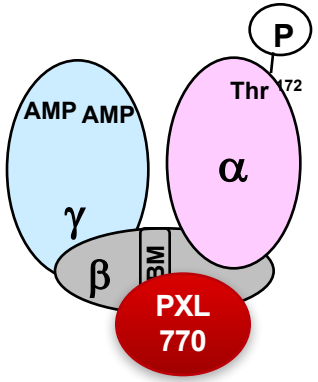
Gluconeogenesis
Glycogen Synthesis
Fatty Acid Synthesis
Triglyceride Synthesis
Protein Synthesis
Cell Cycle

Treatment and Prevention of:

Diabetes
Cardiovascular Disease

PXL770, a Novel Agent for Treating Type 2 Diabetes

- PXL770 is a direct and potent AMPK activator[1]
  - β1 containing heterotrimers: EC50 ~ 50nM
  - β2 containing heterotrimers: EC50 ~ 1µM

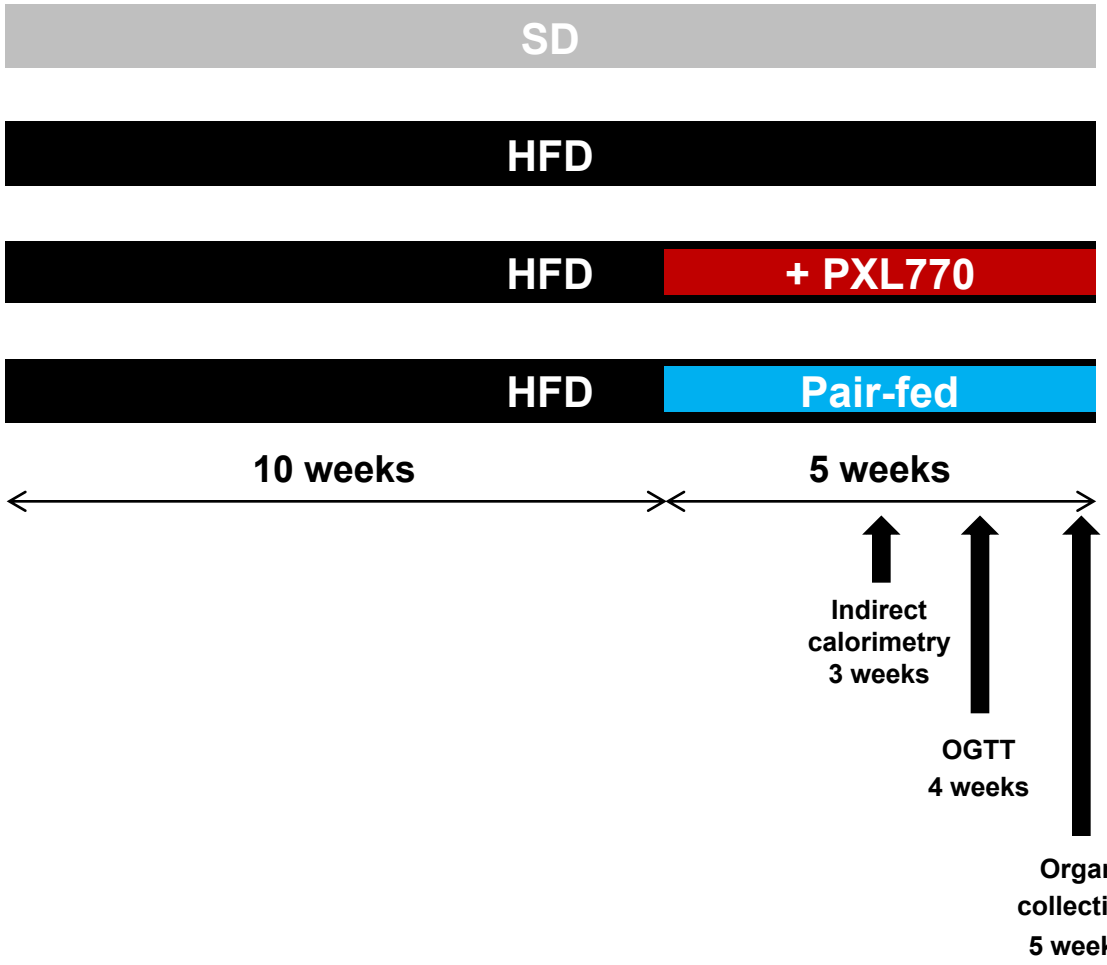


- PXL770 inhibits de novo lipogenesis *in vitro and in vivo* in mice[2]
- PXL770 improves glycemic control, lipid profile and hepatic steatosis in ob/ob mice[1]
- PXL770 is currently in phase I – SAD part completed showing a very good tolerability with no safety signal

[1]Poster 081, World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease, 19th–21st November, Los Angeles, CA, USA
[2]Poster 724, European Association for the Study of Diabetes, 12th–16th September 2016, Munich, Germany

PXL770 Effect in a High Fat Diet Fed Mouse Model

Study Design



Standard Diet (SD) ; n=10

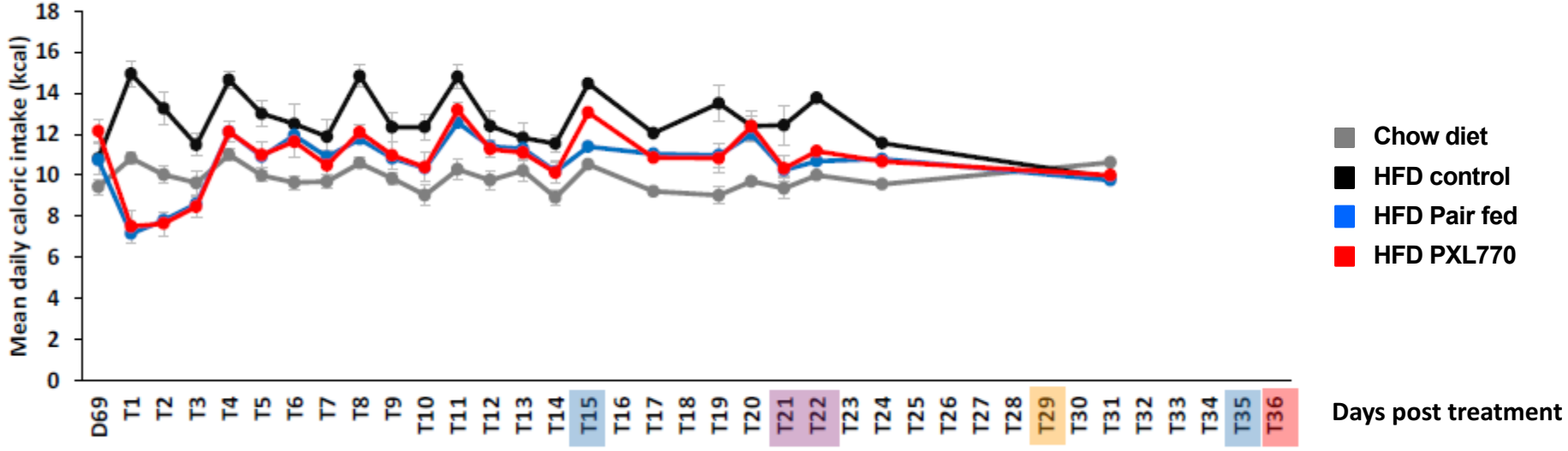
HFD (60% Fat) ; n=10

HFD + PXL770 75 mg/kg BID orally ; n=10

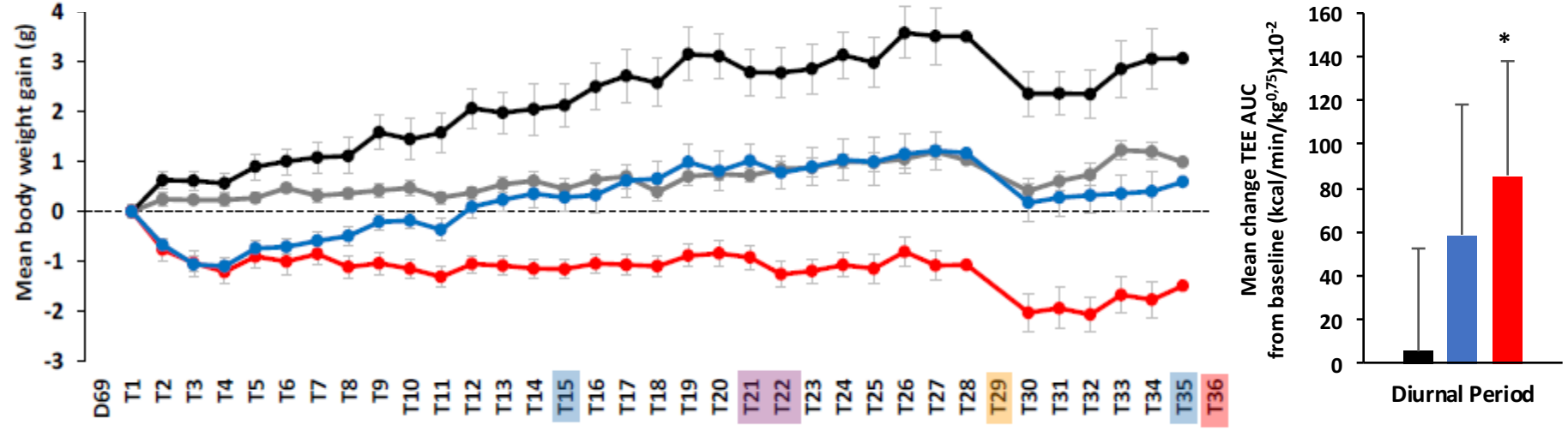
HFD pair-fed ; n=10
same daily caloric intake as PXL770 treated mice

PXL770 Induced a Steady Body Weight Loss Despite Similar Caloric Intake Compared to the Pair-fed Group

HFD mice – 5 weeks of treatment – **Mean daily caloric intake (Kcal)**



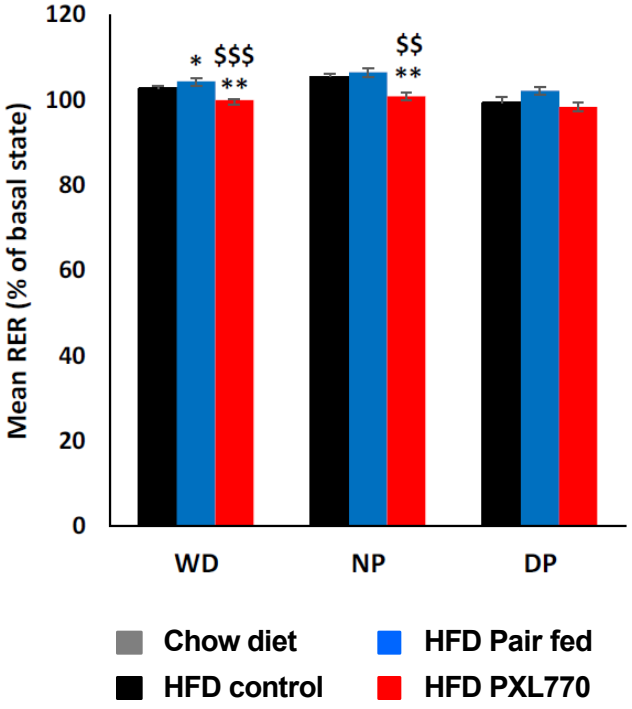
HFD mice – 5 weeks of treatment – **Mean body weight gain (g) & total energy expenditure**



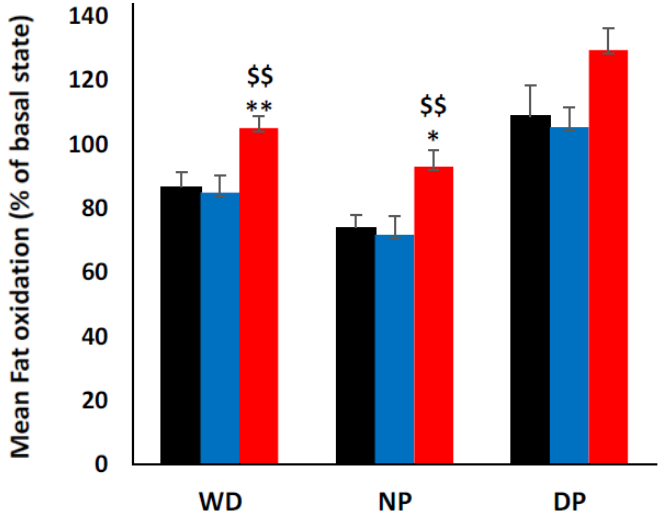
PXL770 Decreases Respiratory Exchange Ratio With an Increase in Fat oxidation in HFD Mice

HFD mice – 3 weeks of treatment – **indirect Calorimetry**

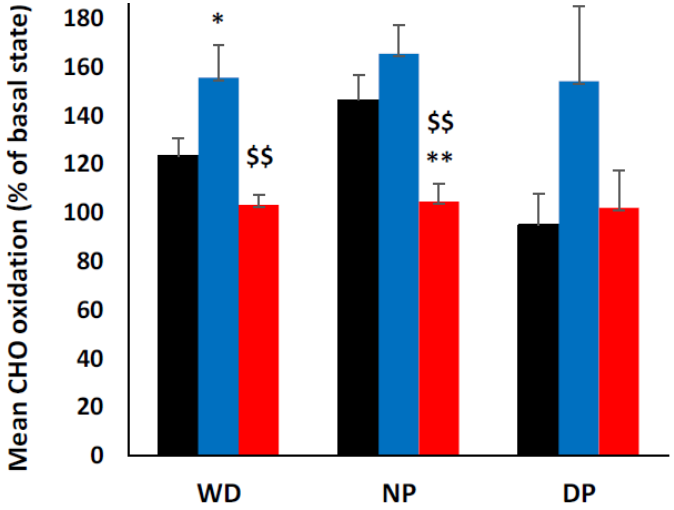
Respiratory Exchange Ratio



Fat Oxidation



Carbohydrate Oxidation



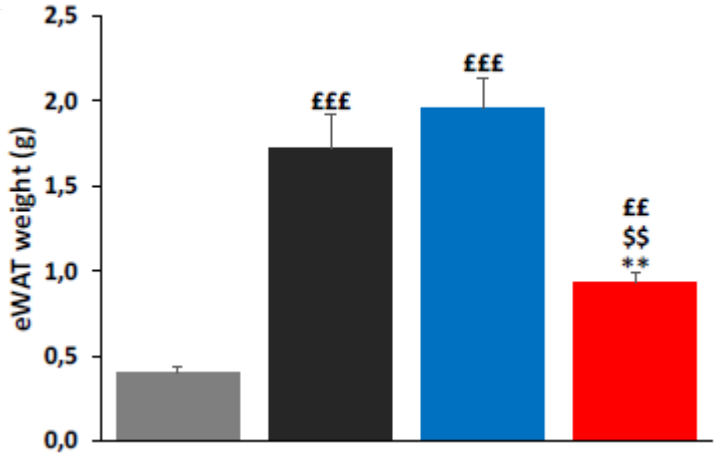
WD: whole day; NP: nocturnal period; DP: diurnal period

Mean ± SEM.
* *P*<0.05, ** P<0.01, vs. HFD control group.
$$ *P*<0.01, $$$ P<0.001 vs. HFD pair-fed group

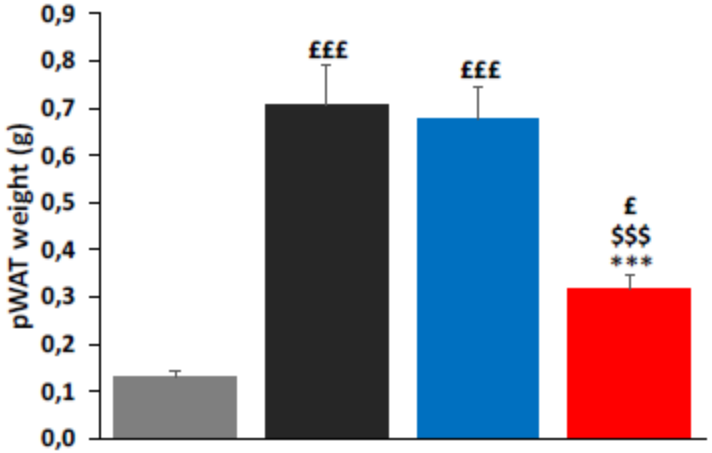
PXL770 Strongly Reduces Fat Mass in HFD Mouse

HFD mice – 5-week treatment – **White Adipose Tissue Weight**

Epidydimal White Adipose Tissue Weight



Perirenal White Adipose Tissue Weight

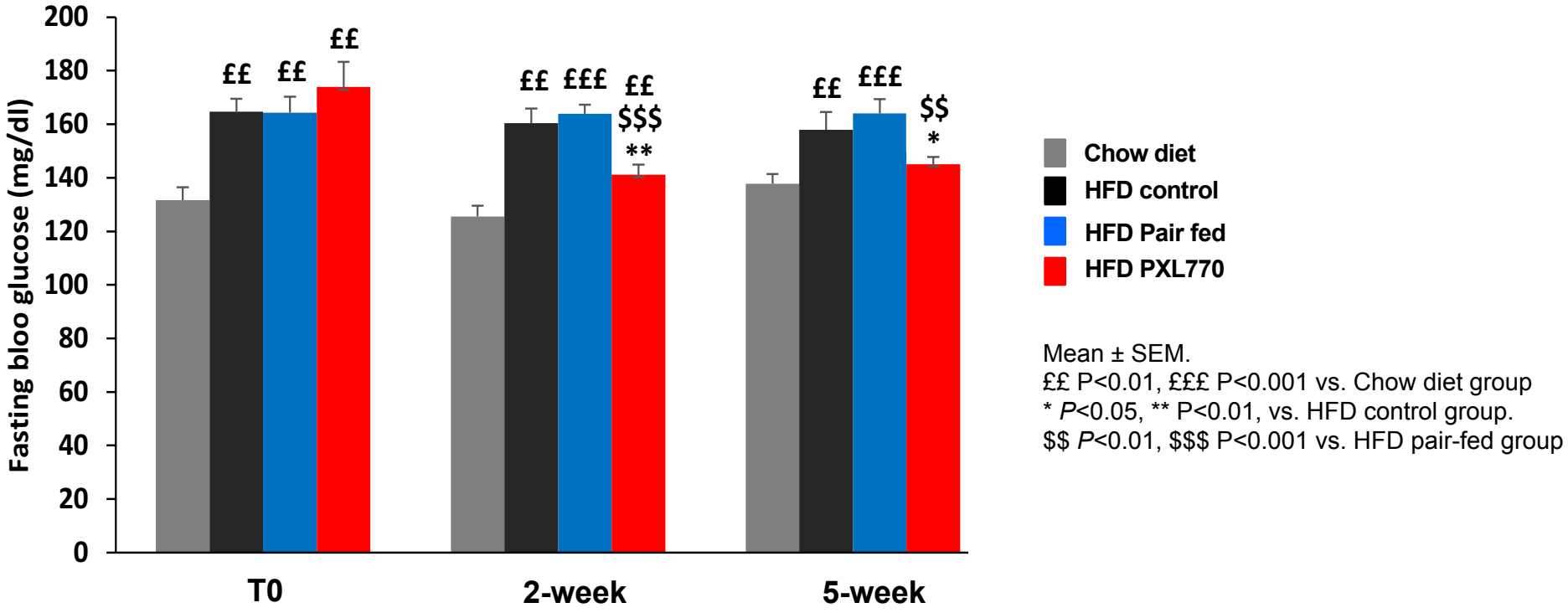


Chow diet
HFD control
HFD Pair fed
HFD PXL770

Mean ± SEM.
££ P<0.01, £££ P<0.001 vs. Chow diet group
* *P*<0.05, ** P<0.01, vs. HFD control group.
$$ *P*<0.01, $$$ P<0.001 vs. HFD pair-fed group

PXL770 Decreases Basal glycemia in HFD Mouse

HFD mice – 2 & 5-week treatment – **3h Fasting glycemia**



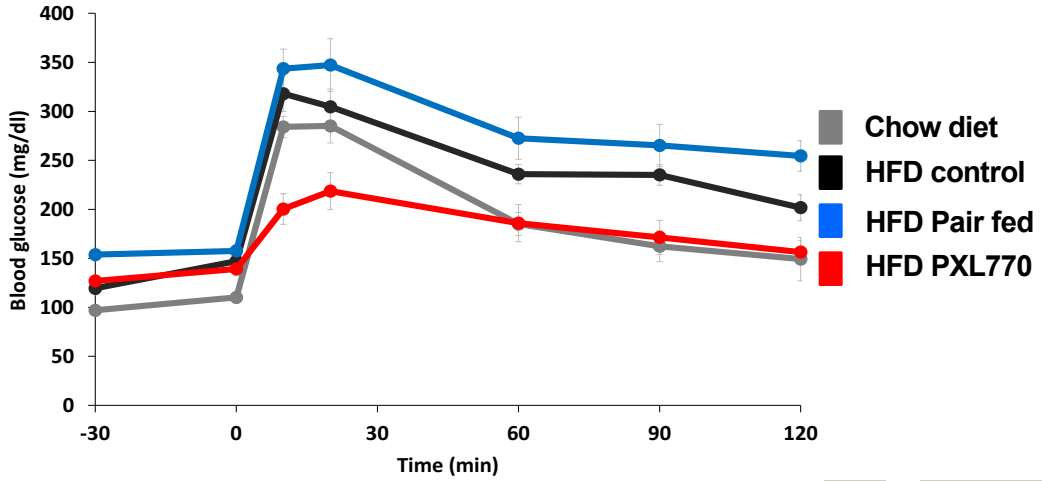
Mean ± SEM.
££ P<0.01, £££ P<0.001 vs. Chow diet group
* *P*<0.05, ** P<0.01, vs. HFD control group.
$$ *P*<0.01, $$$ P<0.001 vs. HFD pair-fed group

- PXL770 induced a significant decrease in basal glycaemia,
  contrary to the pair-fed animals that remained hyperglycemic throughout the experiment.

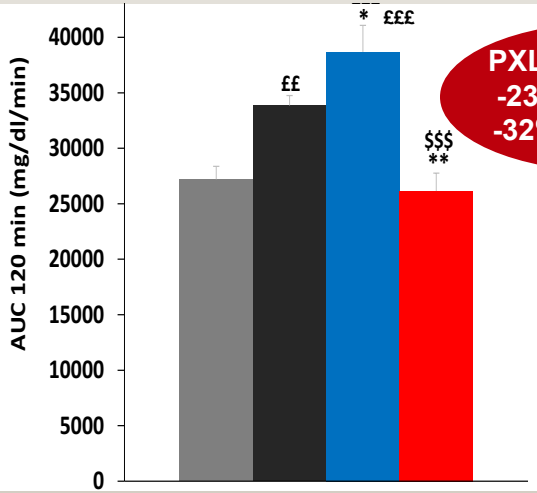
PXL770 Improves Glucose Tolerance in HFD Mouse While Normalizing AUC Insulin

HFD mice – 4-week treatment – **OGTT**

Glucose

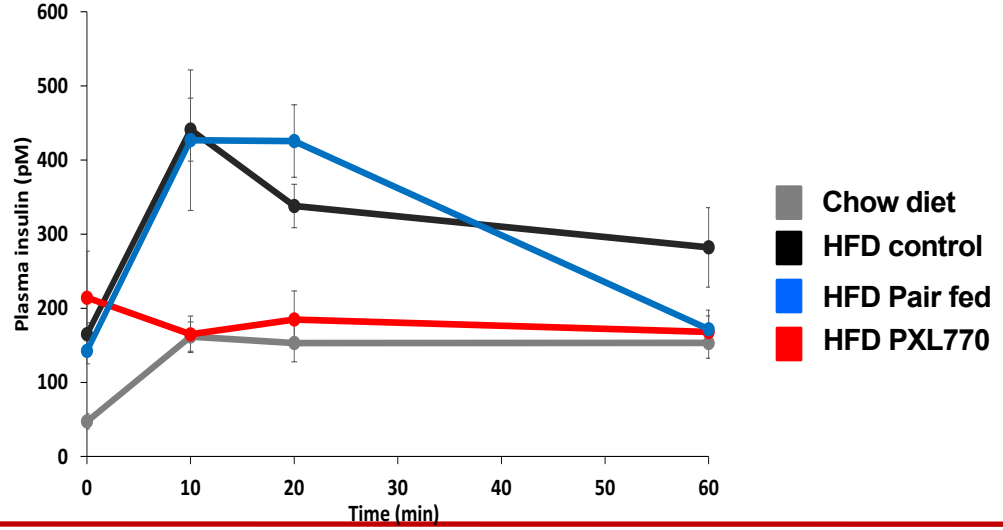


AUC Glucose

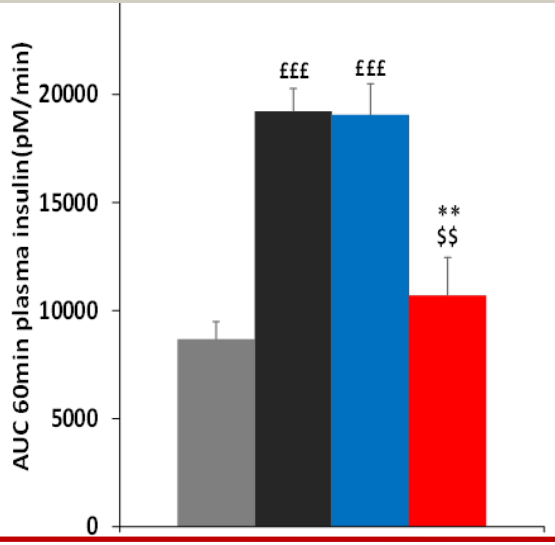


PXL770 75mg/kg
-23% vs. control
-32% vs. pair-fed

Insulin



AUC Insulin



Mean ± SEM.
££ P<0.01, £££ P<0.001 vs. Chow diet group
* *P*<0.05, ** P<0.01, vs. HFD control group.
$$ *P*<0.01, $$$ P<0.001 vs. HFD pair-fed group

Conclusion

In a model of diabetes and obesity:

- PXL770 induces a weight loss
- PXL770 increases energy expenditure and fat oxidation leading to a decrease in fat mass
- PXL770 decreases basal glycemia and improves glucose tolerance

These results

- have been consistently observed in different animal models
- confirm the therapeutic potential of PXL770 for metabolic disorders, such as type 2 diabetes.

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