

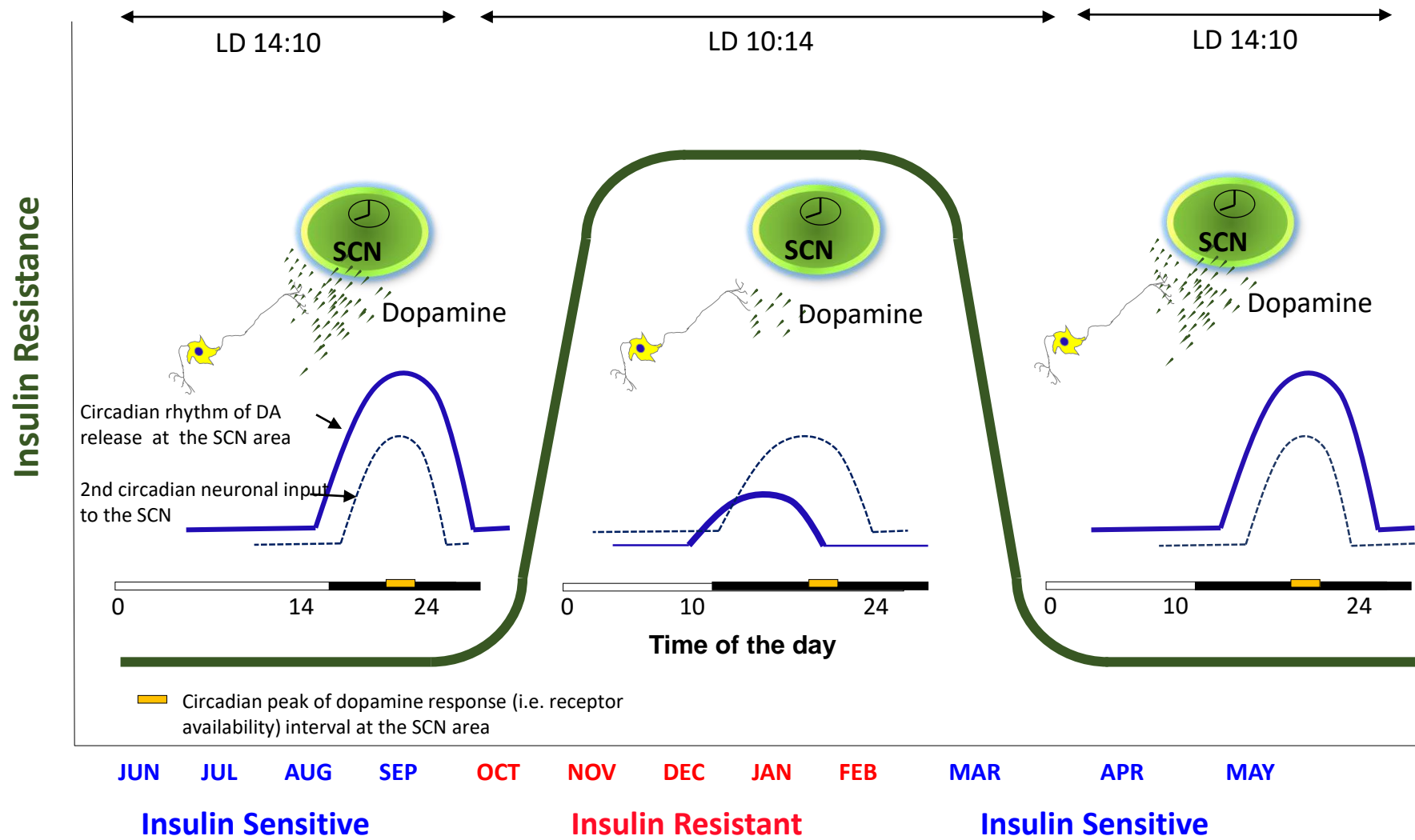


Bromocriptine (BC) Normalizes Elevated Expression of Liver Genes Involved in Fatty Acid Oxidation, Lipogenesis, Inflammation and Endoplasmic Reticulum (ER) Stress and Glucose Intolerance of High Fat/Sucrose Diet Fed Rats

Yahong Zhang, Michael Ezrokhi, Nicholas Cominos, Anthony H. Cincotta

The authors are employees at VeroScience LLC and A.H. Cincotta is a share holder in the company

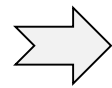
Diminished Circadian Dopamine Peak at the SCN Area Potentiates Naturally Occurring Insulin Resistance in Seasonal Mammals



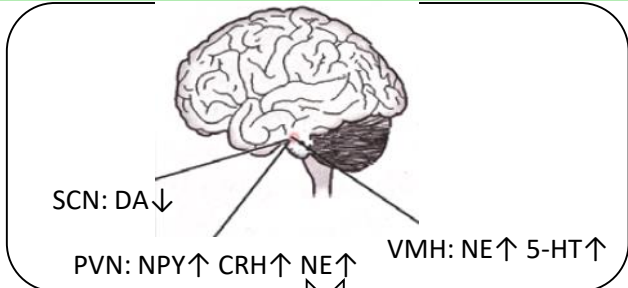
Low Brain Dopaminergic Activity Potentiates Metabolic Syndrome

Western life style

- High fat diet
- Chronic stress
- Disrupted sleep/wake cycle



Low brain dopaminergic activity
(clock region, hypothalamus, striatum)

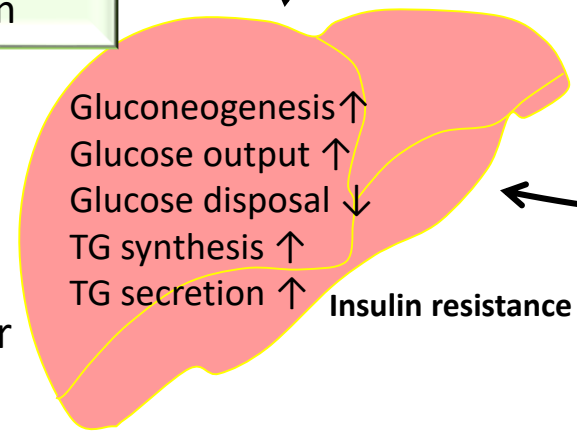
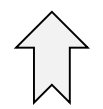


Chronic ↑ sympathetic tone

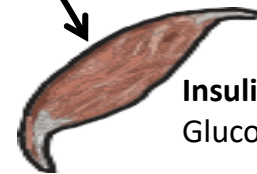
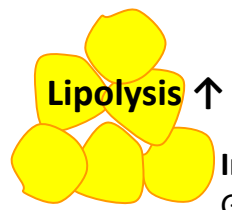
Metabolic syndrome

- Hyperglycemia
- Hyperinsulinemia
- Fattening
- Hyperleptinemia
- Hyperlipidemia
- Hypertension

β-cell insulin secretion ↑
Eventual → → β-cell dysfunction



FFA



References

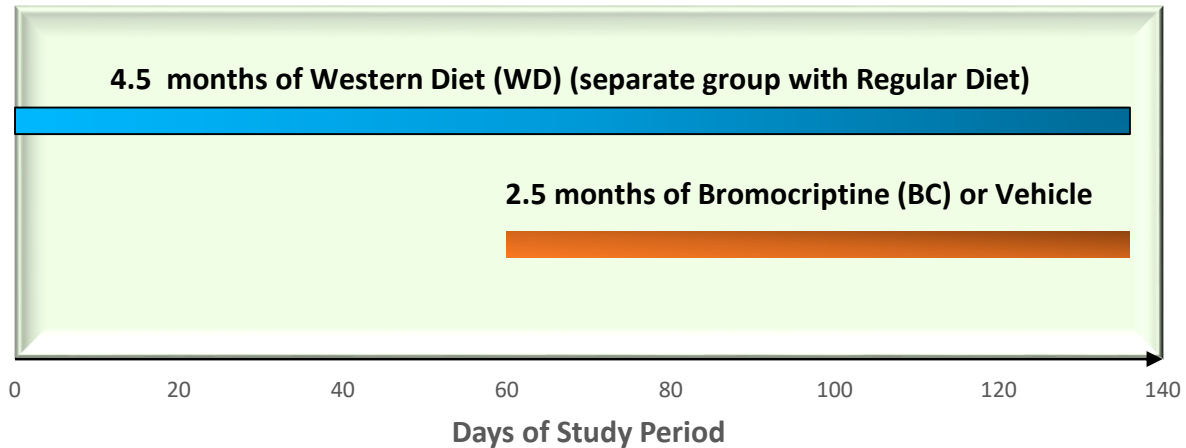
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Long-Term Bromocriptine Treatment for Western Diet-Induced Metabolic Syndrome

Experimental Design

Experimental groups

1. Veh/WD (n=10) 2. BC/WD (n=10) 3. Reg Diet (n=7)



Animals: Female SD rats (11 weeks of age, Taconic Bio), 14:10 hrs light/dark cycle, food and water *ad libitum*

Foods: Western Diet (d12079B, Research Diet – High Fat and Sugar Diet); Regular Diet (2018, Envigo Teklad)

Drugs: Bromocriptine (BC), 7.5 mg/kg, ip, administered daily at 1 hr before light-off; or Vehicle, 0.1ml, ip.

End points

- Glucose Tolerance Test (GTT) was performed at the end of drug treatment.
- Body weight & food consumption were monitored during the study period.
- Liver tissues were collected in liquid N₂ for measurement of
 - Liver Triglyceride (TG)
 - RT-qPCRs of PPAR α , CPT1A, DGAT2, CCL2, DDIT3

PPAR α : transcriptional factor regulates genes involved in fatty acid transport, fatty acid binding and activation, and peroxisomal and mitochondrial fatty acid β -oxidation

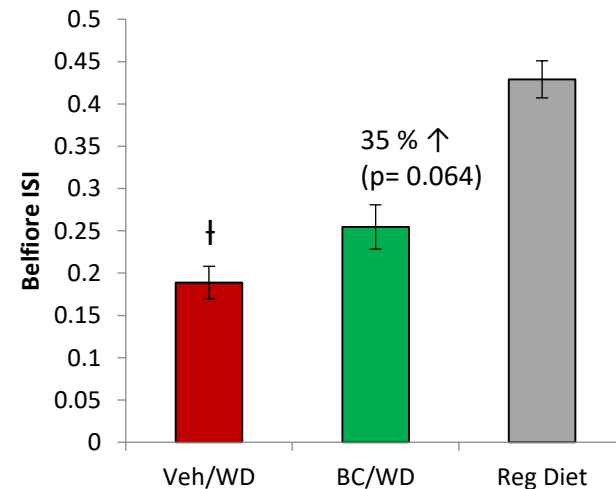
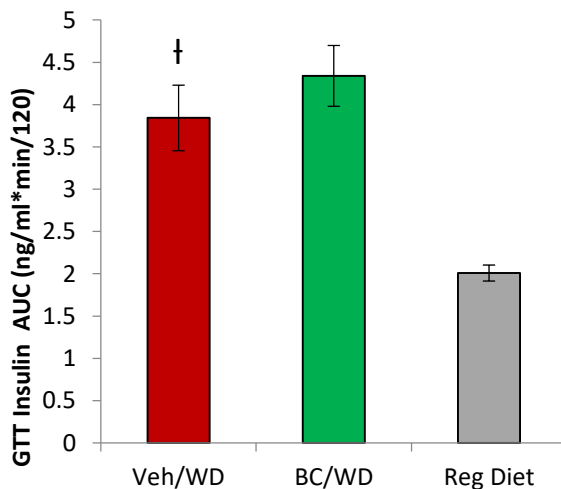
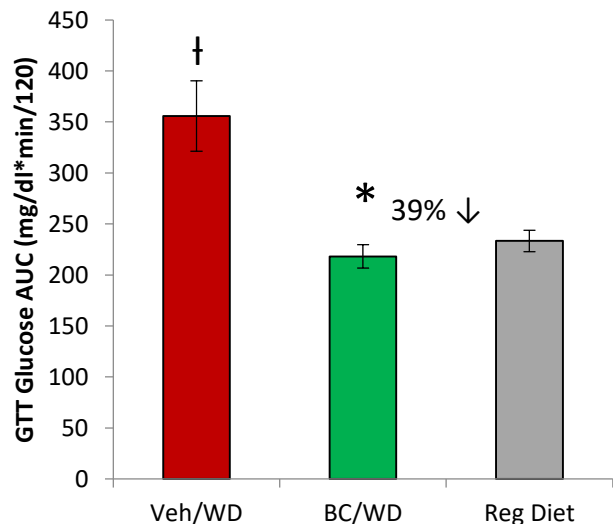
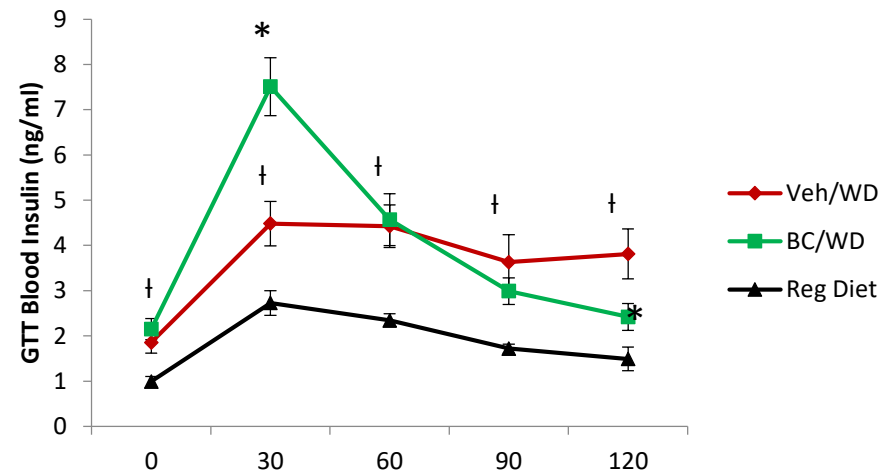
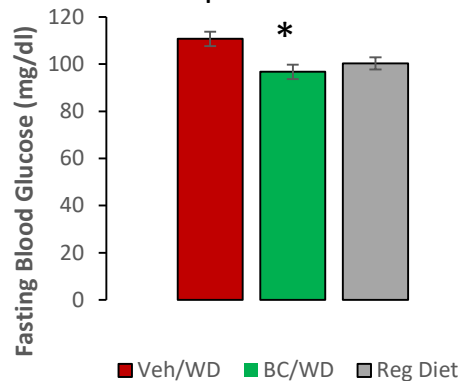
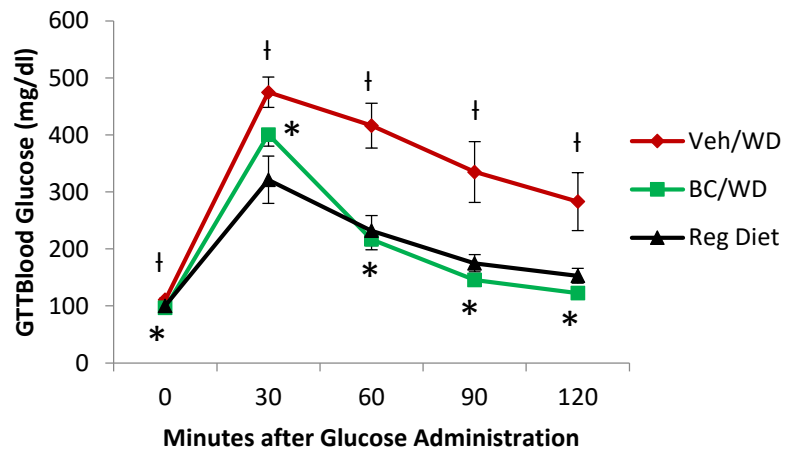
CPT1a: Carnitine palmitoyltransferase 1a, transports long-chain fatty acids cross the inner membrane of mitochondria.

DGAT2: Diacylglycerol O-acyltransferase 2, catalyzes the terminal and only committed step in triacylglycerol synthesis.

CCL2: C-C Motif Chemokine Ligand 2, involved in inflammatory processes with chemotactic activity for monocytes and basophils

DDIT3: multifunctional proapoptotic transcription factor in ER stress response. The protein functions as a dominant-negative inhibitor by forming heterodimers with other C/EBP members, preventing their DNA binding activity.

Circadian Daily Administration of Bromocriptine Improves Western Diet-Induced Glucose Intolerance

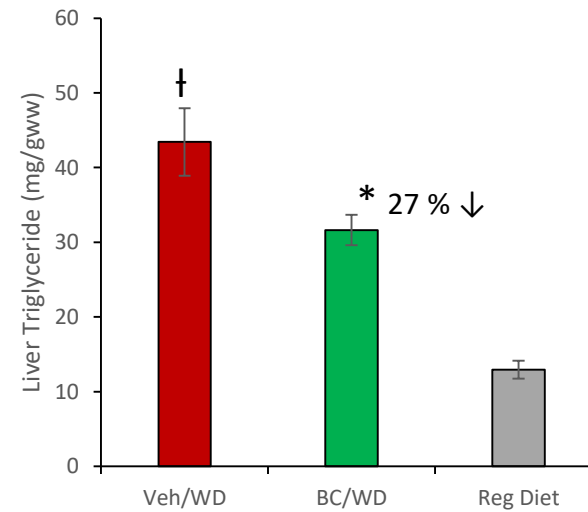
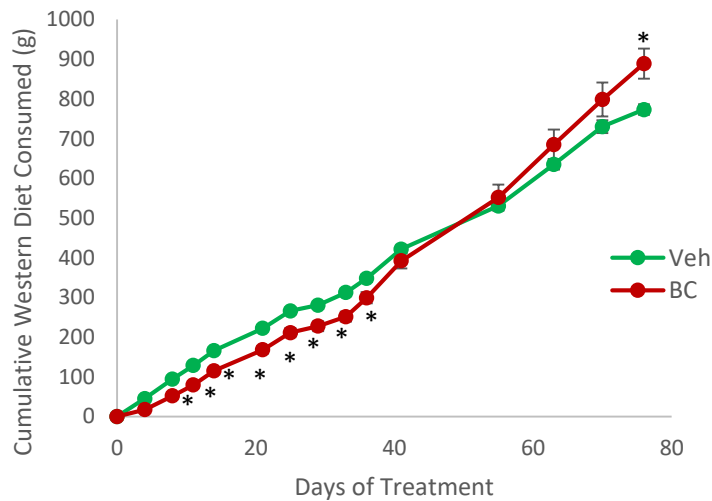
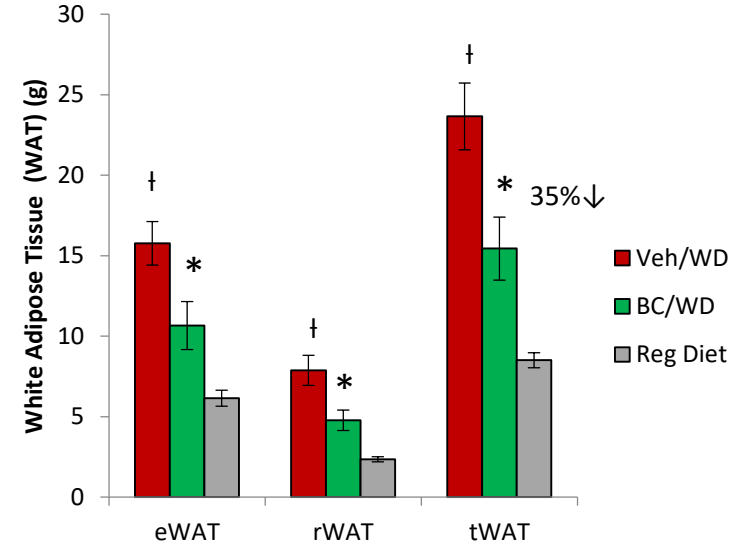
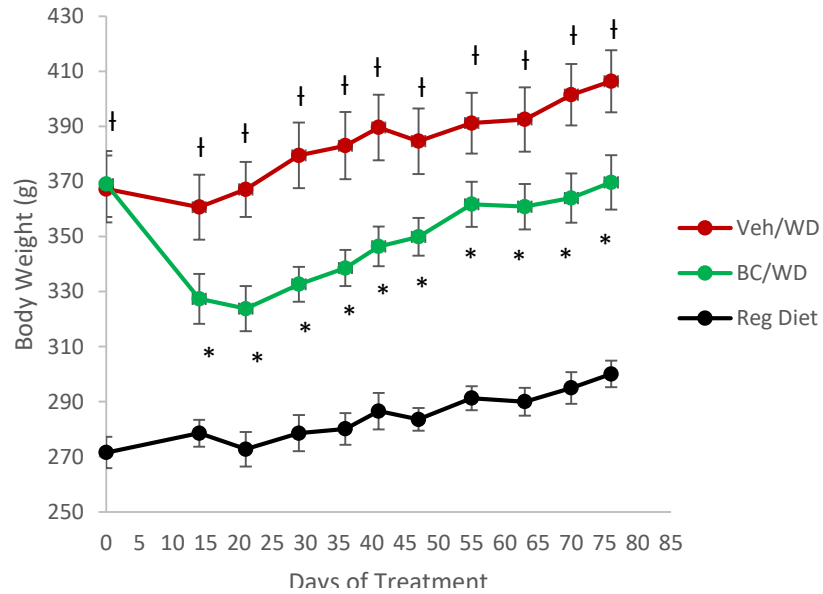


WD: Western Diet, BC: bromocriptine

* P < 0.05 BC/WD vs Veh/WD

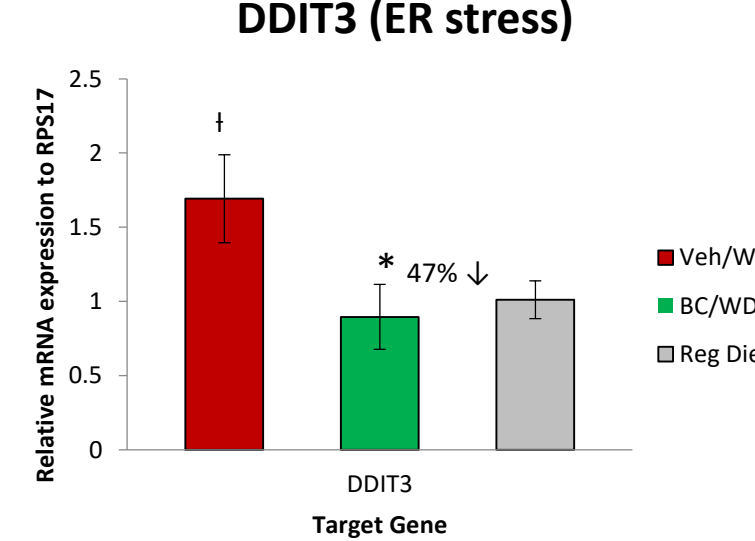
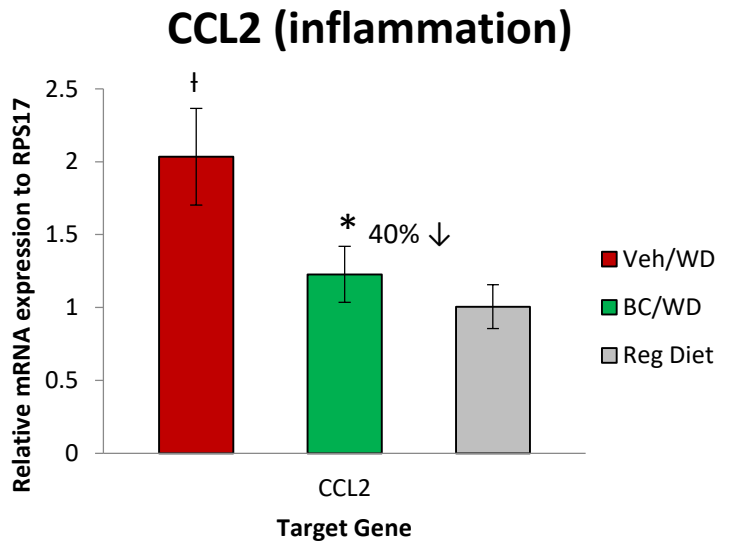
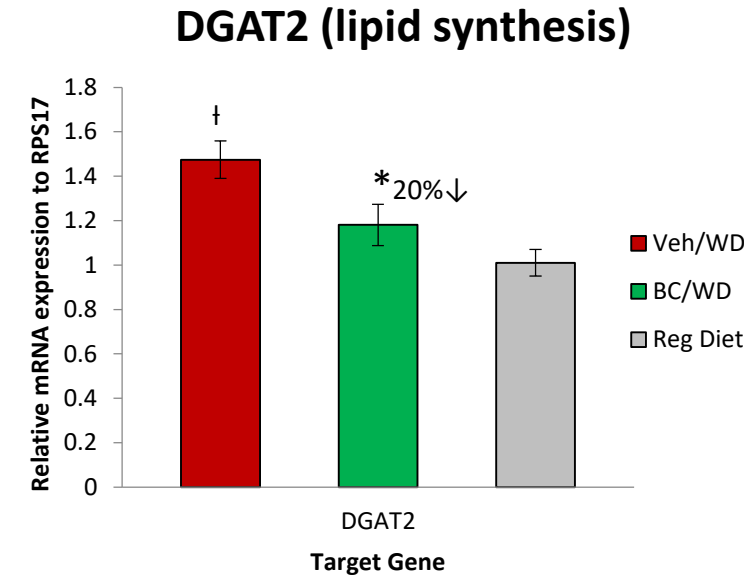
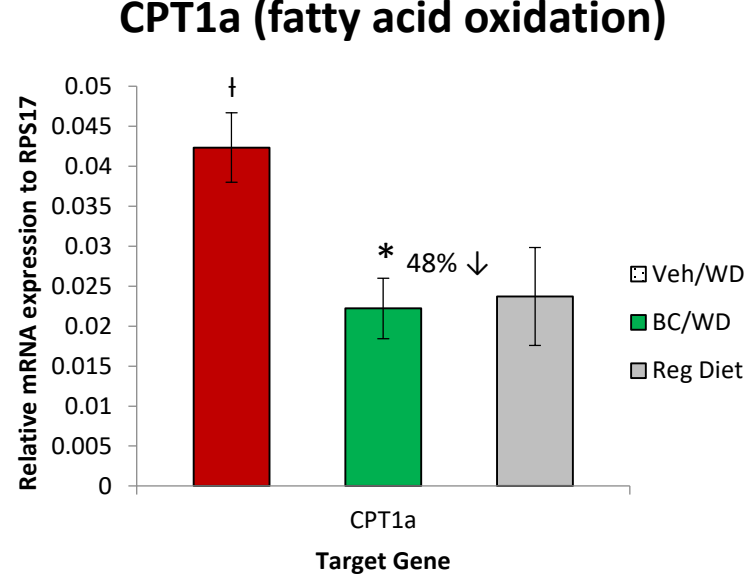
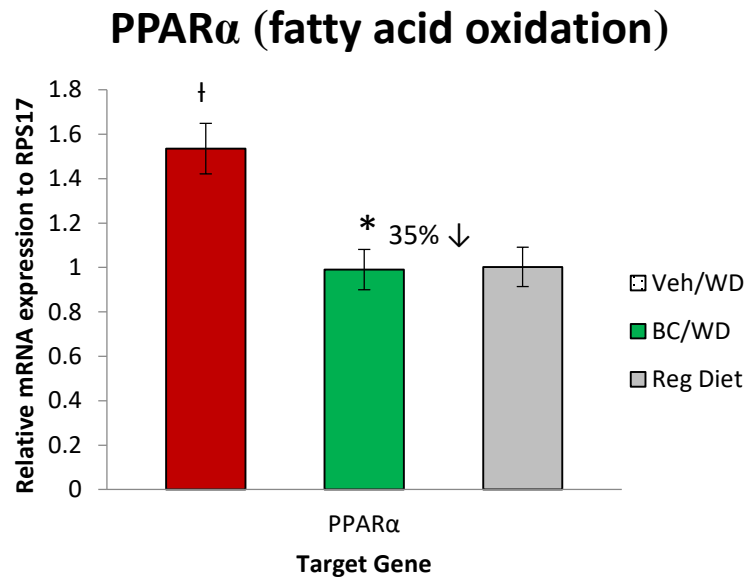
† p < 0.05 Veh/WD vs Reg Diet

Circadian Daily Administration of Bromocriptine Reduces Body Weight, Body Fat and Liver Triglyceride Concentration in Western Diet-Induced Obese Animals



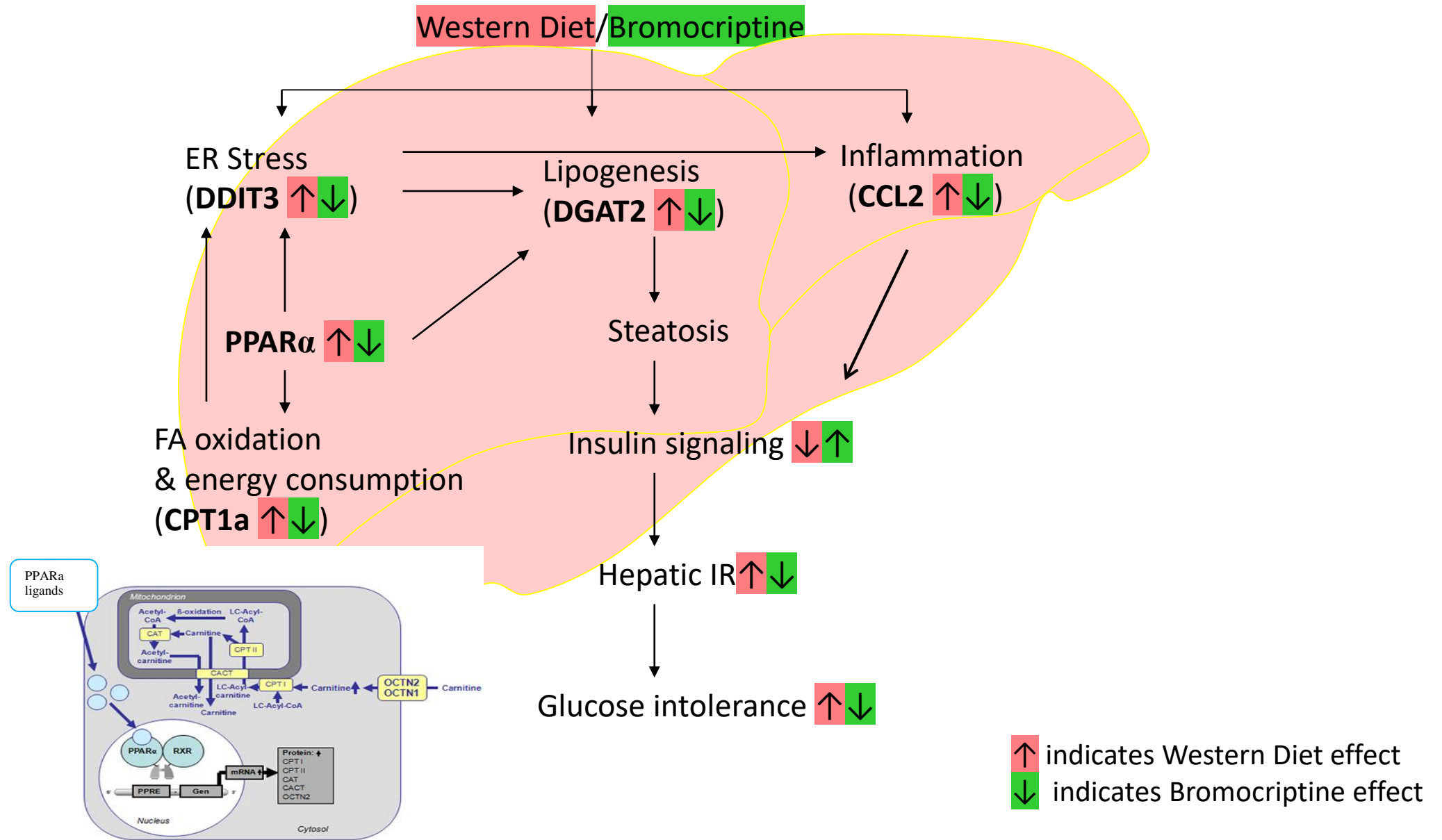
WD: Western Diet
 BC: bromocriptine
 eWAT: epididymal WAT
 rWAT: retroperitoneal WAT
 tWAT: total WAT
 * P < 0.05 BC/WD vs Veh/WD
 † p < 0.05 Veh/WD vs Reg Diet

Circadian-Timed Daily Administration of Bromocriptine Reverses Western Diet-Induced Elevations of Gene Expressions in Hepatic Lipid Synthesis and Oxidation, Proinflammatory and ER Stress Pathways



WD: Western Diet
BC: bromocriptine
RPS17: house keeping gene
* P < 0.05 BC/WD vs Veh/WD
† p < 0.05 Veh/WD vs Reg Diet

Circadian-Timed Bromocriptine Reverses Western Diet-Altered Gene Expressions in Lipid Metabolism, Inflammation, and ER Stress Signaling Pathways in the Liver



Summary

- ❑ Western life style (i.e. Western high fat/sucrose diet) attenuates circadian brain dopaminergic activity and chronically elevates sympathetic outflow to peripheral metabolic organs (i.e. liver, adipose tissue and muscle), overtime resulting in the development of metabolic syndrome.
- ❑ Circadian-timed administration of bromocriptine, an sympatholytic D2 dopamine receptor agonist improves metabolic syndrome.
- ❑ Circadian-timed administration of bromocriptine in Western Diet-induced obese glucose intolerant animals
 - ✓ improves glucose intolerance and insulin response
 - ✓ reduces body weight/body fat and liver triglyceride
 - ✓ reverses Western Diet-elevated hepatic gene expressions in lipogenesis (DGAT2), fatty acid oxidation (PPAR α , CPT1a), inflammation (CCL2) and ER stress (DDIT3) signaling pathways.

Proposed Mechanism of Action of Bromocriptine-QR to Improve Glucose Homeostasis & Insulin Sensitivity in T2DM Human

