Bromocriptine-QR reduces hypertriglyceridemia in hypertensive type 2 diabetes subjects

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Disclosures

- BC, ME and AHC are employees of VeroScience, LLC

Background and Aim

- Chronic sympathetic nervous system (SNS) overactivity is known to cause various adverse metabolic consequences including
  - increased hepatic gluconeogenesis
  - increased free fatty acid mobilization from the adipose tissue
  - inflammation in adipose and liver resulting in insulin resistance
  - beta cell dysfunction resulting from lipotoxicity and glucotoxicity.
- Chronically elevated SNS activity also increases triglyceride levels due to
  - Increased hepatic triglyceride synthesis and secretion
  - Adipose free fatty acid mobilization leading to further hepatic triglyceride synthesis and hypertriglyceridemia
- Hypertriglyceridemia often occurs in the presence of hypertension and this can be a biomarker of chronically elevated SNS activity.
- Bromocriptine-QR (B-QR), a quick-release formulation of micronized bromocriptine, a dopamine agonist, is the only sympatholytic anti-diabetes medication approved for type 2 diabetes (T2DM).
- Preclinical studies have demonstrated that circadian-timed B-QR therapy ameliorates hypertriglyceridemia
- B-QR has been shown to reduce triglyceride levels in obese, hyperinsulinemic subjects without diabetes
- This study evaluated if circadian-timed B-QR reduces triglyceride levels in T2DM subjects with a history of hypertension and with elevated triglyceride levels

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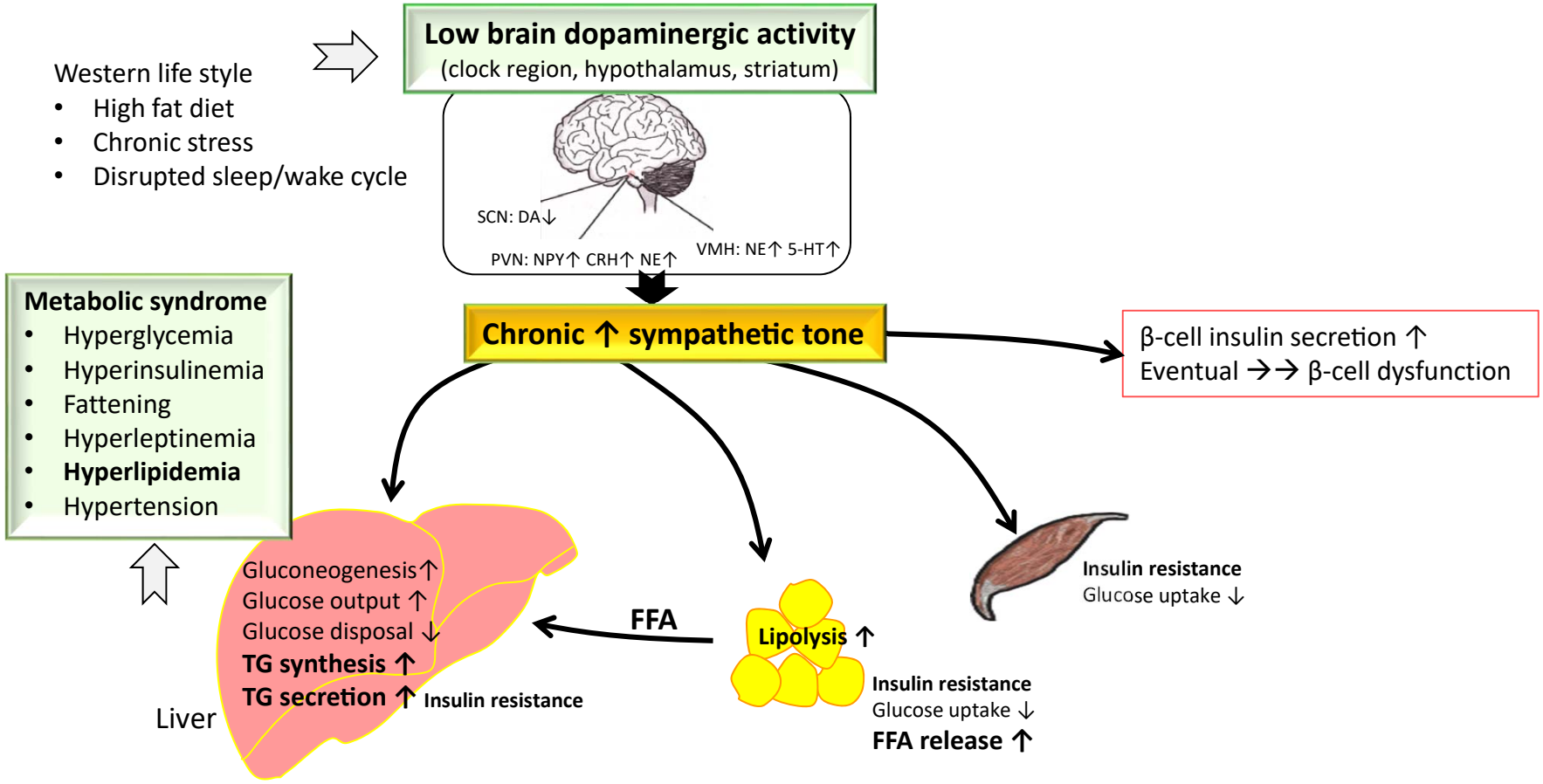
Low Brain Dopaminergic Activity Potentiates Metabolic Syndrome



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Abbreviations:

SCN	Suprachiasmatic nucleus
DA	Dopamine
VMH	Ventromedial hypothalamus
PVN	Paraventricular nucleus
NPY	Neuropeptide Y
CRH	Corticotropin releasing hormone
NE	Norepinephrine
5-HT	5-hydroxytryptamine
FFA	Free fatty acid
TG	Triglyceride

Methods

Study Subjects and Design

- B-QR's effect on triglycerides were analyzed in a subset of subjects (N=378) derived from the Cycloset Safety Trial (CST) with history of hypertension, hypertriglyceridemia (fasting triglyceride level >/= 150 mg/dL) and T2DM with suboptimal glycemic control (HbA1c ≥ 7.0%), randomized to B-QR vs placebo added to standard therapy of diet alone or ≤2 diabetes medications) and completing 24 weeks of study drug treatment.
- The CST was a 12-month multi-center, placebo-controlled, double-blind, parallel-group safety and efficacy study in outpatient subjects with T2DM, randomized 2:1 ratio to B-QR or placebo added to standard therapy (diet ± any one or two antidiabetes medications of sulfonylurea, metformin, thiazolidinedione or insulin). Subjects were required to be on a stable antihyperglycemic regimen for ≥30 days prior to randomization.
- During the first 6 weeks of the trial, the study drug (B-QR vs placebo) was titrated weekly by adding 1 tablet per week (0.8 mg B-QR per tablet) until a maximum tolerated daily dose between 2 and 6 tablets (1.6 to 4.8 mg/day of B-QR) was achieved. The study drug was taken once daily with the morning meal, within 2 hours of waking.

Statistical Analysis

- Between treatment group difference in the change from baseline to week 24 in fasting triglyceride levels was analyzed using Student's t-test
  - Analyses were stratified by baseline triglyceride levels
- Between treatment group difference in the change from baseline to week 24 in HbA1c levels was analyzed using Student's t-test.
  - Analyses were stratified by baseline triglyceride levels

Baseline Characteristics of Study Subjects

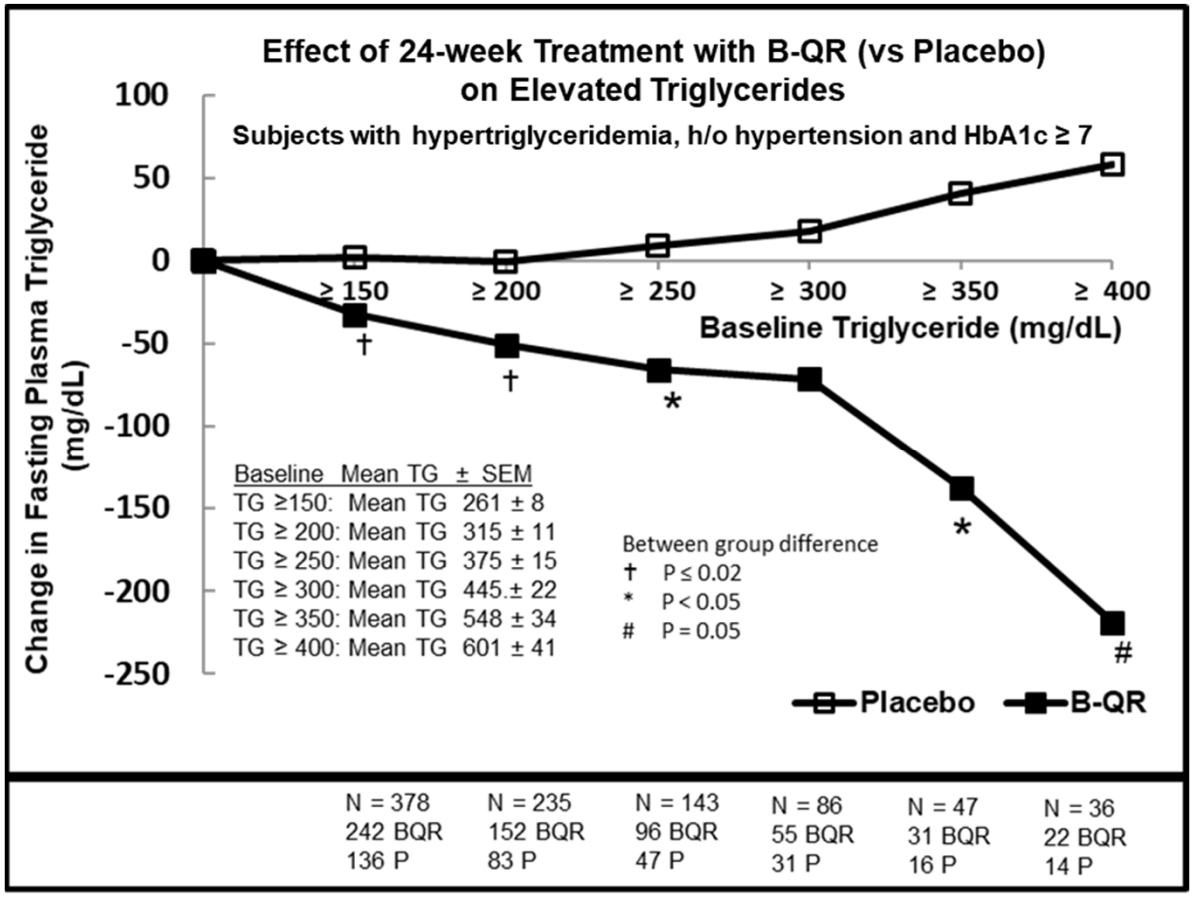
	B-QR (n=242)	Placebo (n=136)
Age (years)	59 ± 0.6	60 ± 0.7
Gender (% male)	66	60
Race (% Caucasian)	75	80
BMI (kg/m^2)	33.7 ± 0.3	33.8 ± 0.4
Duration of Diabetes (years)	9.2 ± 0.5	10.1 ± 0.7
HbA_{1c} (%)	7.86 ± 0.1	7.99 ± 0.1
Fasting Triglyceride	264 ± 9.6	256 ± 11.7
Total cholesterol	189 ± 3.1	182 ± 3.6
HDL	41 ± 0.6	41 ± 0.8
LDL	96 ± 2.4	93 ± 2.8
Resting Heart Rate (bpm)	71 ± 0.7	70 ± 1.0
Systolic BP (mm/Hg)	133 ± 0.9	133 ± 1.2
Diastolic BP (mm/Hg)	78 ± 0.5	78 ± 0.8
Serum creatinine (mg/dL)	1.2 ± 0.0	1.2 ± 0.0

Data are shown as mean ± SEM for continuous variables and % for categorical variables

There were no significant differences in baseline characteristics between the two treatment groups

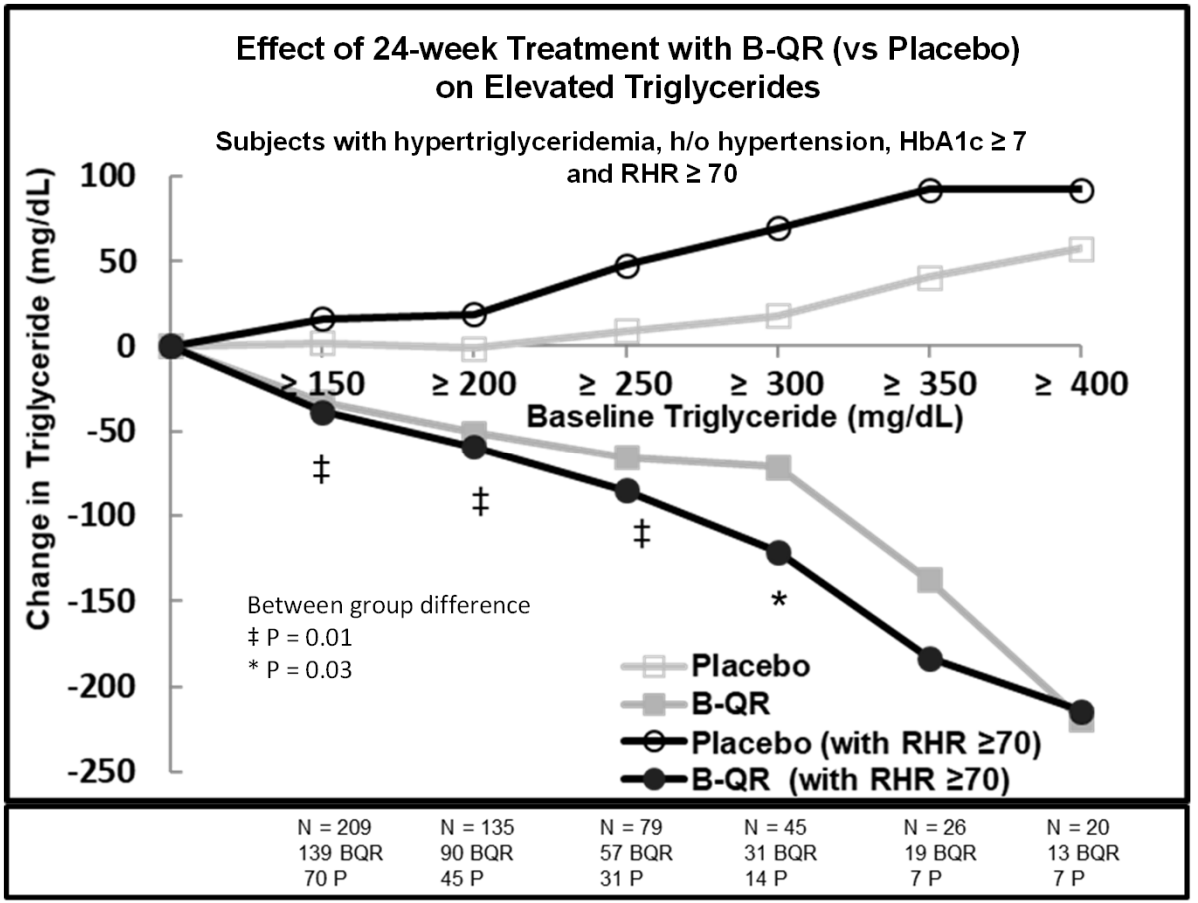
B-QR's Impact on Hypertriglyceridemia in Hypertensive T2DM Subjects with Suboptimal Glycemic Control (HbA1c ≥ 7%)

- B-QR therapy significantly decreased baseline elevated triglyceride levels
- B-QR's effect in reducing baseline elevated triglyceride levels increased with increasing levels of baseline triglycerides



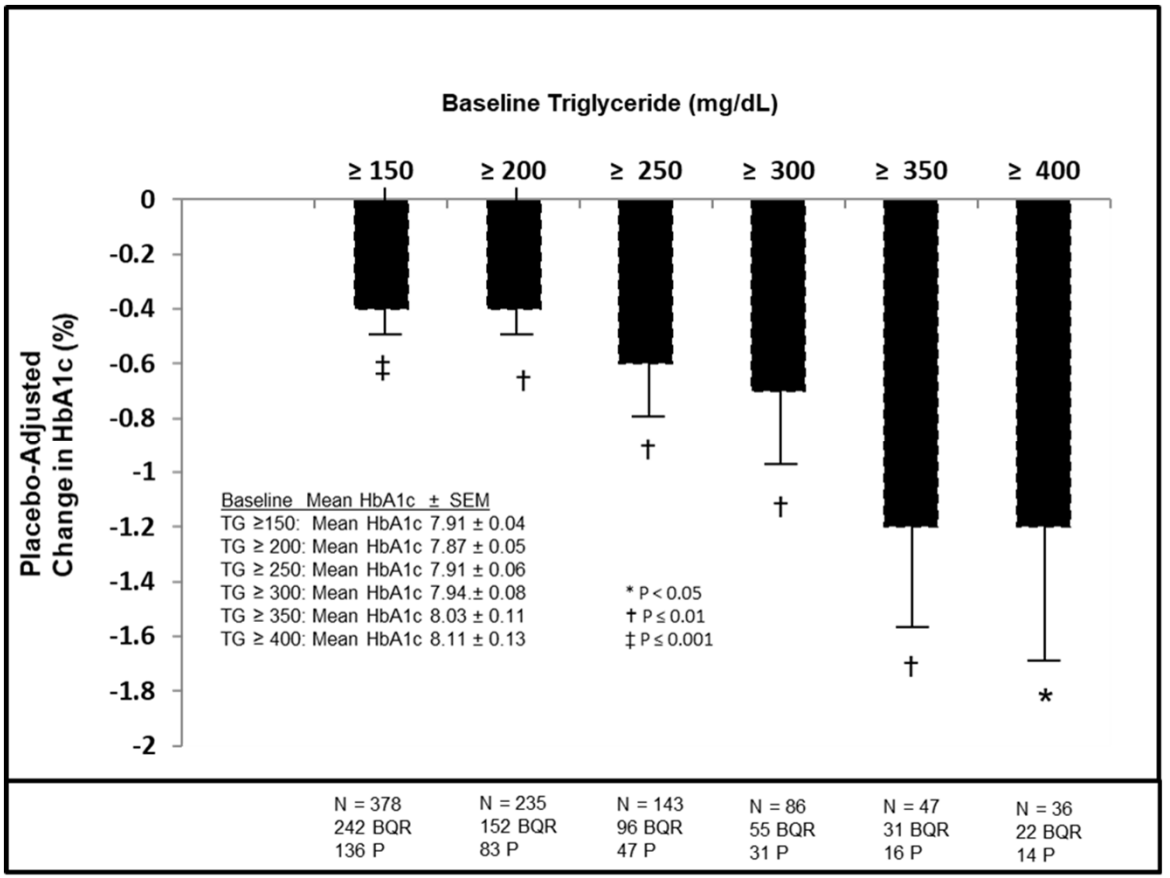
B-QR's Impact on Hypertriglyceridemia in Hypertensive T2DM Subjects with Suboptimal Glycemic Control (HbA1c ≥ 7%) and Elevated Resting Heart Rate

- B-QR's effect in reducing baseline elevated triglyceride levels was greater in T2DM subjects with h/o hypertension and also elevated baseline resting heart rate (RHR) ≥ 70 beats/minute.



B-QR's Impact on HbA1c Categorized by Baseline Triglyceride in Hypertensive T2DM Subjects with Suboptimal Glycemic Control (HbA1c ≥ 7)

- B-QR therapy significantly decreased HbA1c
- B-QR's effect in reducing elevated HbA1c increased with increasing levels of baseline triglycerides



Summary/Conclusions

- Chronic SNS overactivity is known to contribute to hypertension, elevated resting heart rate and hypertriglyceridemia
- B-QR, a sympatholytic dopamine agonist, reduces elevated triglyceride levels in hypertensive T2DM subjects
  - The magnitude of this reduction increases the more elevated the baseline triglyceride level
  - The magnitude of reduction in elevated triglyceride levels is even greater in those with also elevated RHR, another marker of elevated SNS activity.
- The magnitude of HbA1c lowering by B-QR also increases with increasing baseline triglyceride levels.
- The sympatholytic activity of B-QR likely contributes to its effect to reduce elevated triglyceride levels in hypertensive T2DM subjects.