Dopamine agonist effects on hyperglycemia and the cardiometabolic profile

DL Levitt[1], KM Munir[1], EM Lamos[1†]

Affiliation:
[1]Department of Medicine, Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine, 827 Linden Avenue, 2nd floor, Baltimore, MD 21201, USA

† **Corresponding author**:
Address:
Elizabeth M. Lamos, M.D.
Assistant Professor of Medicine
Department of Medicine, Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine
827 Linden Avenue, 2nd floor, Baltimore, MD 21201, USA
Telephone 443-682-6800, Fax 410-856-3846
Email:
elamos@medicine.umaryland.edu

Disclosures: none

1. Abstract:

Dopamine plays a complex role in modulation of cardiometabolic parameters. Positive effects on glucose control and parameters of the metabolic syndrome have been demonstrated in both pre-clinical and clinical data. Pharmacologically, bromocriptine- quick release, a dopamine agonist used for treatment in type 2 diabetes mellitus, provides modest improvement in hemoglobin A1c (HbA1c), weight and lipids. Additionally, bromocriptine has a beneficial overall cardiovascular risk profile. The anti-hyperglycemic effects of bromocriptine are thought to be mediated through the circadian rhythm, but interesting research suggests that central dopamine action may underlie the beneficial cardiometabolic effects. This review will examine the pre-clinical and clinical data regarding known metabolic changes observed with dopamine agonist therapy. The role of prolactin, as a mediator of cardiometabolic risk or a signal of dopamine action, will be discussed.

Keywords: bromocriptine-QR, dopamine agonist, prolactin, type 2 diabetes

Abbreviations: quick release (QR), hemoglobin A1c (HbA1c), type 2 diabetes mellitus (T2DM)

2. Introduction

The role of dopamine in cardiometabolic homeostasis is complex and poorly understood. Dopamine is a neurotransmitter that is peripherally produced within the adrenal medulla as a catecholamine precursor. Because it cannot cross the blood brain barrier, dopamine is also centrally produced and released mainly by the hypothalamus and basal ganglia. Dopamine inhibits the secretion of prolactin from the anterior pituitary gland, giving it the alternate names of prolactin-inhibiting hormone or prolactostatin. Release of dopamine is both induced and tonic. There are five dopamine receptors, which are divided into D1 and D2-like receptors based on their end organ effects. D1-like receptors (D1 and D5) act by activating adenylate cyclase. D2-like receptors (D3, D4, D5) act by inhibiting adenylate cyclase. D1 receptors are the most ubiquitous, followed by D2 receptors. These receptors are found within multiple organ systems including the vasculature (arterial walls), immune system (lymphocytes), kidneys (within the nephron) and pancreas (exocrine and endocrine) (1).

It is hypothesized that dopamine primarily modulates some of the metabolic changes observed in the hibernating animal through altering circadian rhythms. During this state of relative starvation, obesity appears to be beneficial, promoting insulin resistance and lipolysis. In non-hibernation, insulin resistance is reversed. This relationship between reversible insulin resistance and the circadian rhythm is alluded to as the thrifty gene hypothesis (2-4). In humans, it is suggested that the normal physiology of leanness in warm weather and relative obese-ness during cold weather is lost in individuals with type 2 diabetes mellitus (T2DM) because of increased and consistent food intake and subsequent weight. Dopamine's role in these metabolic changes appears more complex as data will be presented which demonstrate the direct effects on insulin sensitivity and lipogenesis/lysis outside of effects on the light/dark cycle.

Given the multiple possible cardiometabolic targets for dopamine action, it is not surprising that dopamine agonism in the central nervous system may mitigate the effects of diabetes mellitus and metabolic syndrome. Bromocriptine is predominantly a dopamine D2 receptor agonist, alpha-1 receptor antagonist, and alpha-2 agonist (5). Bromocriptine is manufactured in both quick-release and a sustained-release formulation. The sustained release therapy is

approved to treat prolactinomas, pituitary tumors, and Parkinson's disease. However, bromocriptine mesylate quick-release (-QR, Cycloset®, Ergoset®) is approved only for T2DM treatment (6).

Not approved for use in T2DM, cabergoline, a highly specific central dopamine D2 agonist traditionally used for treatment of hyperprolactinemia, has also been studied in patients with hyperglycemia. Additionally, favorable glycemic and cardiometabolic effects observed in prolactinoma patients after treatment with either bromocriptine or cabergoline suggest that central D2 receptor agonism or reducing prolactin levels may underlie the mechanism of the cardiometabolic effects (7).

Section 3 Pre-clinical studies

Multiple rodent models have been used to investigate dopamine actions via bromocriptine administration on metabolic parameters including weight, lipids, and glucose homeostasis. The ob/ob mouse is a classic T2DM animal model. Ob/ob mice cannot produce leptin, leading to obese mice with hyperglycemia and hyper-insulinemia. Other diabetic models include overfeeding and db/db mouse model (a leptin receptor gene mutation). Type 1 diabetes mellitus models include the administration of alloxan or streptozocin (both toxic to pancreatic beta cells) or the non-obese diabetic mouse (NOD) model. Many study designs dosed bromocriptine or comparator treatment using a light/dark cycle.

When intraperitoneal bromocriptine and SKF 38343 are administered toyoung ob/ob mice early in the light cycle, both individually improve cardiometabolic para-meters and when combined demonstrated a significant reduction in body weight, body fat, food consumption, triglycerides, free fatty acids as well as serum glucose and plasma insulin when compared to lean mice (all $p < 0.05$) (8).

These results are similar to a second study that also showed a decrease in glucagon when bromocriptine and SKF38343 are administered to ob/ob mice, there was a decrease in hexokinase activity and basal cAMP associated with a decrease in basal insulin release which may be the result of decreased exposure to glucose, free fatty acids and triglycerides (9).

Bromocriptine and SKF treated ob/ob mice demonstrated improved hyperphagia, weight gain and glycemic control compared to lean mice. Treated ob/ob mice significantly reduced their food consumption by approximately 33% compared to untreated ob/ob mice

($p<0.0001$). While plasma corticosterone levels were three times higher in ob/ob mice compared to lean mice, treated ob/ob mice corticosterone levels decreased by 65%. Interestingly, in post-mortum brain slices, neuropeptide Y, a potent orexigenic agent, levels were significantly reduced in multiple brain centers including the suprachiasmatic nucleus, intergeniculate nucleus, para-ventricular nucleus, and arculate nucleus of treated ob/ob mice compared to lean mice. Corticotropin-releasing hormone, which has been shown to promote central insulin resistance, was also significantly decreased in the paraventricular nucleus and dorsomedial hypothalamus in treated ob/ob mice compared to lean mice (10).

In another study, bromocriptine and SKF treated ob/ob mice reduced their food consumption by 55% within 24 hours of treatment. An increased oxygen cons-umption was observed and was associated with a decreased respiratory quotient reflecting decreased lipogenesis. Additi-onally,

DHEA, known to inhibit body fat accumulation, increased by one-third in treated ob/ob mice compared to untreated ob/ob mice. Xylulose-5-phosphate, known to stimulate glycolysis, levels were significantly higher in treated ob/ob mice compared to untreated ob/ob mice ($p<0.01$) (11).

Post-mortem islet cell evaluation in bromocriptine and SKF treated ob/ob mice demonstrated increased GLUT2 immuno-reactivity, decreased glucokinase immuno-reactivity and beta-cell hyperplasia compared to untreated mice. Treated mice demonstrated a 3.5-fold increase in islet cell insulin content, correlating with a greater than 50% reduction in plasma insulin levels compared to untreated ob/ob mice (12).

In a slightly longer duration than those performed in ob/ob mice, Rats with metabolic syndrome, induced by over-feeding with a high fructose solution, experience lower systolic blood pressure, normalize weight, and decrease food and water intake when treated with bromocriptine compared to untreated rats. Additionally, serum glucose, triglycerides and insulin levels were also lower in those treated with bromocriptine. Myonecrosis and lymphocytic infiltration were noted in cardiac tissue of rats untreated with bromocriptine (13).

In db/db mice treated with bromocriptine and SKF demonstrated lower food consumption, lower free fatty acid levels and lower blood glucose levels compared to untreated mice. However,

unlike the ob/ob mice, insulin levels were higher, but hypertrophy of pancreatic islets and subsequently reduced glucose-mediated insulin release were improved (14). In NOD mice administered bromocriptine, both male and female mice demonstrated rapid onset of hyperglycemia which resulted in a rapid decrease in insulin, a biphasic increase in glucagon and increased corticosterone levels. Metoclopramide, a D2 receptor antagonist, was able to reverse the bromocriptine-induced hyperglycemia (15).

In a therapeutic study of rats treated with alloxan, bromocriptine and bromocriptine plus glipizide treatment demonstrated significant improvement in blood glucose levels compared to untreated rats (16). In a complex study, STZ treated mice that were administered prolactin had less hyperglycemia and reduced insulitis incidence compared to mice not treated with prolactin (17). This study suggested that prolactin may modulate the early mechanisms implycated in auto-immune T1DM.

These data suggest that D1 and D2 receptor agonism has direct effects on insulin processing and release. These changes likely mediate the secondary effects observed on nutrient processing, lipids and glucose levels in different models of diabetes mellitus. The central modulation of neuropeptide Y and corticosterone-releasing hormone may be co-players with dopamine in modulating food consumption and thus weight. However, the interplay of dopamine in autoimmune diabetes remains poorly understood.

Section 4. Clinical studies

Bromocriptine-QR is a second-line oral anti-hyperglycemic agent. Dosing should be initiated between 0.6-1.8 mg per day, and uptitrated to 4.8 mg per day as tolerated (6, 18). It is recommended to be administered within 2 hours of awakening, reflecting the hypothesis that bromocriptine may be resetting the circadian clock (19). Bromocriptine-QR is associated with a modest HbA1c reduction (-0.4-1%) as well as beneficial effects on weight, blood pressure, and lipid levels (6). Additionally, a significant risk reduction in composite cardiovascular outcomes has also been demonstrated (20). Refer to figure 1 to review bromocriptine's cardiometabolic benefits.

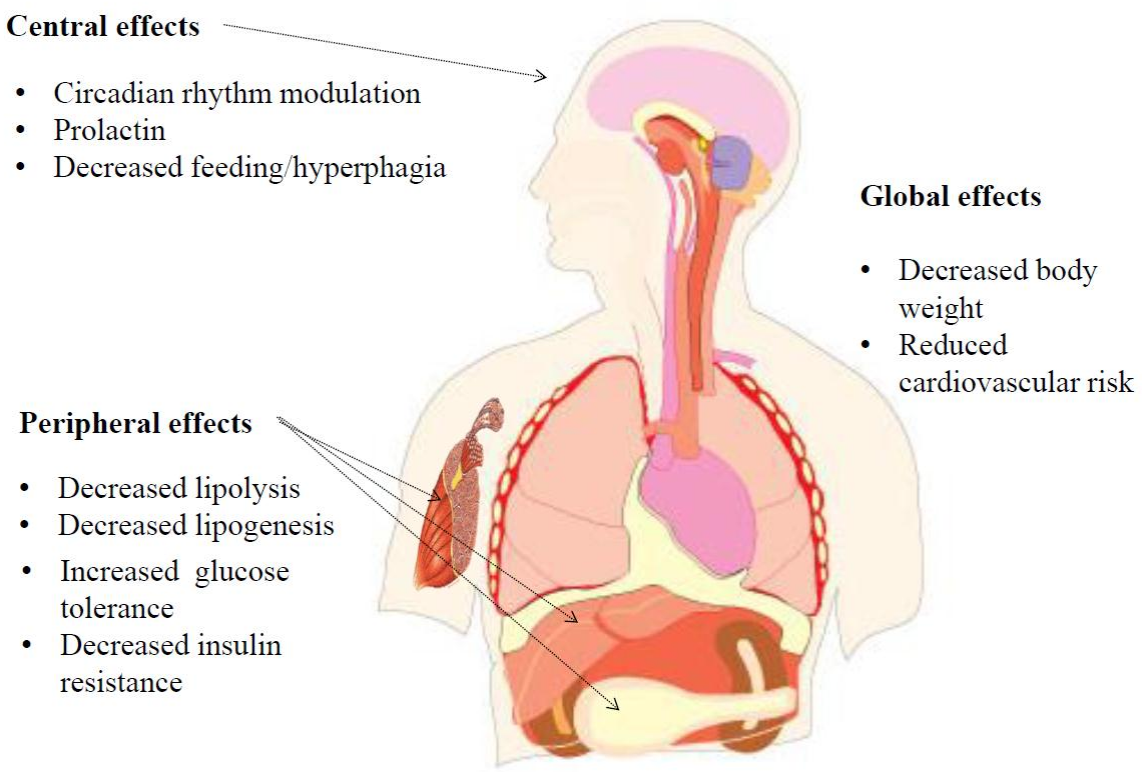

Figure 1: Effects of bromocriptine.

Section 4.1 Glycemic effects

Patients with baseline poor glycemic control receive the most benefit from bromocriptine-QR. When used as monotherapy in overweight (BMI > 25 kg/m^2) individuals with poor glycemic control (baseline HbA1c 8-9%) compared to diet alone, HbA1c reduction of 0.4% occurred. However, almost one-third of bromocriptine-treated patients experienced a 1.0% HbA1c reduction (6). Obese subjects treated with bromocriptine-QR demonstrate improved response to oral glucose tolerance testing (21), in addition to reduced fasting plasma glucose (22). Bromocriptine-QR does not improve postprandial glycemic control (23). During the Cycloset Safety Trial, hypoglycemia was infrequent, experienced by 0.2% in the treatment arm and 0.4% in the placebo arm (24).

Metformin is superior as mono-therapy compared to bromocriptine-QR, for moderately controlled T2DM. When bromocriptine-QR is used as add-on therapy to metformin, there is a trend toward decreased HbA1c and fasting plasma glucose, compared to bromocriptine-QR

monotherapy (25). When combined with sulfonylurea therapy, bromocriptine-QR may lead to more potent glycemic control.

In a 24-week study, obese T2DM patients were randomized to receive either a weight neutral diet with bromocriptine-QR plus sulfonylurea, compared to sulfonylurea monotherapy. At completion, combined therapy led to 0.6% HbA1c reduction ($p < 0.0001$) and 23 mg/dl fasting plasma glucose reduction ($p<0.0002$), compared to sulfonyl-urea monotherapy (26).

As an adjunct to thiazolidinedione therapy, bromocriptine-QR has demon-strated 0.8% HbA1c reduction ($p = 0.001$) and 22 mg/dl fasting plasma glucose reduction ($p = 0.03$) when baseline HbA1c $\geq$ 7.5%. Glycemic improvement is not as dramatic with tighter baseline glycemic control (27). When used as an adjunct to insulin, bromocriptine-QR treatment does not improve HbA1c, unless baseline HbA1c > 7.5% (25).

Cabergoline use has been demonstrated to promote glycemic benefits in a small study. When studied in 17 overweight individuals with uncontrolled T2DM (10 treated subjects, 7 placebo subjects) for 3 months, cabergoline led to 0.8% HbA1c reduction, compared to placebo (28).

Section 4.2 Metabolic effects

When bromocriptine-QR is used as monotherapy to treat T2DM, 0.2 kg weight gain is reported (6), compared to 0.9 kg weight gain when used as an add-on therapy to sulfonylurea therapy (26). When bromocriptine-QR is used as an adjunct to thiazolidinedione therapy, lower extremity edema and weight gain were not reported (27).

Bromocriptine can decrease body fat, leading to weight loss. 33 obese post-menopausal non-diabetic women received bromocriptine within 7 hours of awakening for 6 weeks. 8 of 33 subjects received bromocriptine 1.25 mg each day, while the other subjects received 2.5 mg daily. It is noted that 26 of 33 subjects had estradiol implants during this study, which could confound outcome results. Skinfold thickness measurements were conducted in four areas to measure body fat composition: suprailiac, triceps, biceps, and subcapsular. After 6 weeks of treatment, there was 8.6 lb fat loss reduction per individual, demonstrated by 25% reduced suprailiac skinfold thickness, 26% reduced triceps skinfold thickness, 31% reduced biceps

skinfold thickness, and 20% reduced subcapsular skinfold thickness (29).

To demonstrate fat loss in a double-blind randomized study, 17 obese individuals (>25% body fat for men, >30% body fat for women) were randomized to receive bromocriptine-QR 1.6 – 2.4 mg or placebo at 8AM daily for 18 weeks. In addition to study drug, subjects were instructed to maintain a moderate caloric restricted diet. At baseline, 2 subjects in the bromocriptine-QR group had diabetes, compared to 3 subjects in the placebo group. Both groups experienced decreased body fat and weight due to the caloric restricted diet. After 2 weeks, the bromocriptine-treated group continued to lose body fat, while the placebo group did not. After 18 weeks, body weight decreased in the bromocriptine-treated group by 6.3 ± 1.5 kg, compared to 0.9 ± 1.0 kg decrease with placebo ($p < 0.01$). Both serum glucose and insulin levels were blunted during oral glucose tolerance testing in the bromocriptine-treated group (30).

Bromocriptine-QR has inconsistently demonstrated modest blood pressure and cholesterol reduction during clinical studies. In a subset of the Cycloset Safety Trial, there was a 1.76 mmHg decrease in systolic blood pressure ($p = 0.0099$) and 1.19 mmHg decrease in diastolic blood pressure in the bromocriptine-treated group, compared to placebo ($p = 0.0038$). No significant change in cholesterol profile or heart rate was reported in this study (31). In another study, when 13 non-diabetic, hyperinsulinemic obese women were given maximally tolerated bromocriptine-QR (3.2 ± 0.4 mg daily) for 8 weeks, total cholesterol decreased by 7% ($p < 0.05$). Cholesterol reduction was in the setting of decreased free fatty acid and triglyceride levels. There was not a statistically significant difference in VLDL, LDL, or HDL cholesterol (32).

Interestingly, dopamine antagonism is associated with weight gain and hyperglycemia. This is most notable with use of anti-psychotic agents (33-35). The mechanism behind the metabolic derangements is not understood and the contribution from lowering dopamine levels (and in some cases with conventional anti-psychotics associated with elevated prolactin levels) is unclear.

When using dopamine agonist therapy to treat hyperprolactinemia, there is subsequent improvement in waist circumference, body weight, cholesterol, HbA1c, and insulin resistance as measured

by HOMA-IR (7), most notably in male patients (36). While the etiology of gender differential benefit is unknown, it has been verified by a second study (37). Alternatively, dopamine antagonism leads to worsening of the cardiometabolic state, promoting weight gain and insulin resistance (33-35).

Prediabetic prolactinoma patients treated with cabergoline for 6 months noted 15% triglyceride reduction ($p < 0.05$), 27% free fatty acid reduction ($p < 0.01$), 25% IGF-1 reduction ($p < 0.01$), 20% hsCRP reduction ($p < 0.01$), 18% HDL cholesterol increase ($p < 0.05$), and 35% 25-hydroxyvitamin D increase, compared to matched prediabetic patients with hyperprolactinemia. Cabergoline treatment did not affect total and LDL cholesterol or fasting glucose levels (38). In a 4-month study, 27 hyperprolactinemia patients treated with bromocriptine were divided into 2 groups: (1) 12 patients with persistently elevated prolactin, (2) 15 patients with normalized prolactin levels on treatment. When given metformin (2.55 – 3 g daily) for 4 months, patients with persistent hyperprolactinemia experienced slight improvement in prolactin levels, in addition to improving insulin resistance (as measured by HOMA-IR), 2-hour post-challenge plasma glucose, and triglycerides (39).

Section 4.3 Cardiovascular effects

During the Cycloset Safety Trial, the composite cardiovascular endpoint, defined as composite of the first myocardial infarction (MI), stroke, coronary revascularization, or hospitalization for angina or congestive heart failure, occurred in 1.9% of bromocriptine-treated patients, compared to 3.2% given placebo, resulting in a 40% relative risk reduction (HR 0.61, 95% CI 0.38 – 0.97, $p = 0.02$). Fewer patients underwent coronary revas-cularization in the bromocriptine-treated group (0.44%), compared to placebo (1.08%), resulting in a 57% relative risk reduction approaching significance (HR 0.43, 95% CI 0.18 – 1.03). Within 30 days of study drug use, 4 bromocriptine-treated patients died, compared to 2 placebo patients. All deaths were attributed to a cardiovascular etiology (20).

In well-controlled T2DM patients, bromocriptine-QR can further decrease the incidence of cardiovascular outcomes. 1,834 subjects from the Cycloset Safety Trial (1,219 bromocriptine-QR, 615 placebo) had a baseline HbA1c $\leq 7.0\%$. After 52 weeks of treatment, the composite cardiovascular

disease endpoint occurred in 19 bromocriptine-treated patients (1.6%) and 19 control patients (3.1%), generating a 48% hazard risk reduction (HR 0.52, 95% CI 0.28 – 0.98) (20).

There is an association between hyperprolactinemia and atherosclerosis, endothelial dysfunction, all-cause and cardiovascular mortality (40-41). Of the 3,929 subjects evaluated in the Study of Health in Pomerania study, those with the highest prolactin levels experienced the highest all-cause mortality risk (men HR 1.75, 95% CI 1.32 – 2.32; women HR 1.66, 95% CI 1.08 – 2.56, $p < 0.05$). Amongst the highest prolactin tertile, the multivariable-adjusted HR for cardiovascular death was prominently elevated (men HR 2.16, 95% CI 1.27 – 3.67; female HR 2.84, 95% CI 1.38 – 5.89, $p < 0.045$) (42).

Section 5. Discussion

T2DM rodent models demonstrate consistent reduction in weight, triglyceride, free fatty acid, and blood pressure when administered both D1 (i.e. SKF) and D2 (i.e. bromocriptine) agonist therapy. Clinical studies using bromocriptine-QR as a sole agent also lead to modulation in cardiometabolic parameters, but not as consistently as in the rodent model. It is possible that the lack of D1 agonist therapy during clinical trials may explain the less impressive clinical results. Moreover, most mouse models were administered intraperitoneal bromocriptine, which is likely metabolized differently than oral bromocriptine administered during clinical studies.

Dopamine may be one of the modulators of cardiovascular disease, in the setting of obesity and diabetes mellitus. Bromocriptine-QR modestly reduces HbA1c and may lead to decreased composite cardiovascular outcomes, even in patients with good glycemic control. It can be used successfully as add-on therapy to metformin or a sulfonylurea treatment. While the mechanism underlying cardiovascular risk reduction is not well understood, animal and clinical studies have shown varying benefits including modulating weight, cholesterol, and insulin resistance which are especially important in a high cardiovascular risk population. However, the use of bromocriptine-QR may be limited by side-effects.

During the Cycloset Safety Trial 3,070 T2DM patients were enrolled in a 52-week safety and efficacy trial. At baseline, patients were allowed to take up to 2

diabetes medications, including insulin. 47% of bromocriptine-treated patients discontinued study treatment, compared to 32% placebo discontinuation. 32% of all bromocriptine-treated patients reported nausea, compared to 7.6% given placebo. Other common adverse drug reactions included emesis, dizziness, headache, and diarrhea (24).

Dopamine appears to have peripheral and central actions that beneficially modulate cardiometabolic parameters. It remains unclear if this is due to direct dopamine receptor action or potentially modulation of prolactin as a metabolic co-player. If prolactin is not a direct participant, then prolactin maybe an interesting biomarker for cardiovascular risk. Interestingly, in addition to dopamine agonist use, metformin has been demonstrated to mildly decrease prolactin levels in the setting of hyperprolactinemia, further reinforcing the link between prolactin and metabolic syndrome (39).

Section 6. Summary

Dopamine agonist treatment, specifically bromocriptine-QR, has the potential to improve contribute to the T2DM cardiometabolic imprint. This is supported in pre-clinical and clinical data as well as in individuals with hyperprolactinemia. Although gastro-intestinal side effects limit its broad use, bromocriptine-QR provides beneficial cardiometabolic outcomes in a high cardiovascular risk population.

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