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REVIEW ARTICLE

BROMOCRIPTINE: A NOVEL APPROACH FOR MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Quick release formulation of Bromocriptine mesylate is recently been approved by FDA (Food and Drug Administration) for the treatment of type 2 diabetes mellitus. Early morning dose of bromocriptine mesylate reduces the plasma prolactin level and increases the hypothalamic dopaminergic drive thereby reducing postprandial plasma glucose, triglyceride, and free fatty acid concentrations. Conventional preparations of bromocriptine are available in 2.5 mg or 5 mg tablets used for hyperprolactinemia and suppression of lactation. Studies have shown that quick release bromocriptine given in dose of 0.8-4.8 mg per day for a period of 6 month has successfully achieved target blood sugar. So the drug is well tolerated in antidiabetic dosage with mild side effects like nausea vomiting and fatigue. The central mechanism of action , good side effect profile and its effects to reduce adverse cardiovascular outcomes make it an attractive option for treatment of type 2 diabetes.

Key words: Bromociptine, diabetes, insulin resistance, quick release formulation, prolactin

INTRODUCTION

India currently leads the world in number of people with diabetes. The Diabetes Atlas published by the International Diabetes Federation shows there are currently over 40 million diabetic patients in India. These numbers are predicted to increase to 69 million by 2025[1]. Furthermore, India occupies the second position with respect to the number of patients with impaired glucose tolerance (IGT)[2]. By the year 2025, India shall have the maximum number of diabetics in the world making it, the "Diabetic capital of the world"[2]. The prevalence of the disease in adult is 2.4% in rural and 4.0 - 11.6% in urban dwellers[2-4].

The increased prevalence is attributed to the aging population structure, urbanization, the obesity epidemic, and physical inactivity. These changes are more obvious in urban residents who consume 32% of energy from fat as compared with 17% in rural residents[5].

Psychological stress, depression, and short sleeping hours, which have become increasingly common in developing countries undergoing rapid economic developments, have been associated with higher risk of the metabolic syndrome and diabetes in Asian population[6].

Diabetes mellitus refers to a group of common metabolic disorders that shares a phenotype of hyperglycemia. Once regarded as a single disease entity diabetes is now seen as a heterogenous group of disease characterized by a state of chronic hyperglycemia resulting from a diversity of etiologies, environmental and genetic acting jointly[1]. While Type I diabetes is an autoimmune disease which results into pancreatic beta cell death and resultant lack of Insulin production, Type II diabetes is scientifically most challenging disease, which is characterized by elevated insulin resistance and glucose intolerance. Type II diabetes can occur as a result of dysfunction in glucose, lipid and energy homeostasis in organs/organ systems including liver, adipose, muscle, gastrointestinal tract. Elevated levels of serum glucose and free fatty acids occurring due to imbalances in lipid and carbohydrate metabolism then leads to endoplasmic reticular stress in pancreatic beta cells, leading ultimately to pancreatic beta cell death (terminal diabetes).

Despite the great understanding of pathophysiology and meticulous efforts towards management of diabetes, the disease and related complications are still increasing due to multiple defects. The aim of the management of diabetes is to maintain euglycemia and prevention of various micro and macro-vascular complications of diabetes mellitus.

Various modalities available for the management of diabetes are :-

- Diet restriction
- Exercise
- Drugs:- these includes oral hypoglycemic drugs and insulin.

Among oral hypoglycemic drugs insulin secretagogue (like sulfonylurea, meglitinide derivative), insulin sensitizer thiazolidinediones (like pioglitazone, rosiglitazone) and Biguanides (like Metformin) and α Glucosidase inhibitors (Acarbose, Miglitol). Also there are some recently developed drugs like amylin agonist (Pramlintide), analog of glucagon like peptide-1(GLP-1 analog eg. Exenatide and Liraglutide), and Inhibitor of Dipeptidyl peptidase-4 (DPP-4 inhibitor eg. Sitagliptin).

Inspite of all these commomly used drugs,the research is still going on for an ideal antidiabetic with minimal side effects and better compliance . In this line other mechanisms of diabetes pathophysiology is being searched exhaustively. One such mechanism is "role of hypothalamus and neurohormonal circuitary in glycemic control " which incorporates the cross talk between blood born factors and neurons. This theory emphasizes that altered circadian neuroendocrine rhythm (Dopamine, 5-HT

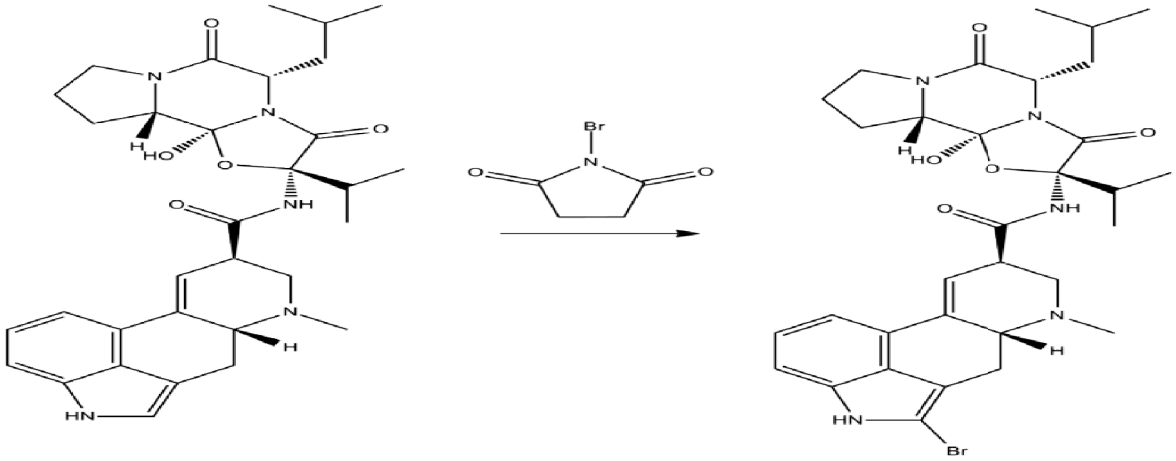
and Norepinephrine) in the hypothalamus is seen in diabetes mellitus[7,8]. Studies shows that reduced central dopaminergic tone has a pivotal role in the development of diabetes mellitus. So, dopaminergic agonists may help in resetting the altered dopaminergic tone and thus it can be of help in controlling diabetes mellitus.

BROMOCRIPTINE

Bromocriptine mesulate quick release formulation has been approved by FDA for the treatment of diabetes mellitus in adultas an adjunct to diet and exercise to improve glycemic control.

Chemistry: Bromocriptine,(ie. 2-bromoergocriptine, is a semisynthetic derivative of a natural ergot alkaloid, ergocriptin (a derivative of lysergic acid), which is synthesized by bromination of ergocriptin using N-bromosuccinimide.

The structural formula of bromocriptine is shown in figure. Bromocriptine mesylate is a white or slightly colored, fine crystalline powder with a molecular formula of $C_{32} H_{40} Br N_5 O_5 CH_4 SO_3$ and a molecular weight of 750.72.



Ergocriptin **Bromocriptine**

Mechanism of action: Bromocriptine is a sympatholytic D2 dopamine agonist. This acts as a centrally acting antidiabetic agent and reduces plasma glucose, triglyceride and free fatty acid levels, and also has some cardioprotective action. A quick release formulation of Bromocriptine, administered within two hours of awakening, is believed to augment low hypothalamic dopamine level and inhibit excessive sympathetic tone within central nervous system, resulting in decrease in plasma glucose level[7,9].

Background: The idea of using bromocriptine for the treatment of type 2 diabetes came while studying the metabolism of migrating birds. It was noted that their hypothalamus have the ability to develop seasonal insulin resistance by controlling their metabolism. There is differential processing of fuel during different part of the day[7]. Also, when food availability is low during the harsh winter month, birds develop an insulin resistant or glucose intolerant state so that thare is increased basal lipolytic activity and spared glucose utilization in peripheral tissues and increase hepatic glucose output that helps in proper functioning of CNS. This CNS mediated increase in hepatic glucose output protects the brain against glucopenia[7,10].

Metabolically, the excess insulin production, decreased resistance to insulin, and elevated cholesterol levels helps them in storing the excess energy they are consuming that is necessary for the expected hibernation or migration. Thus the final benefit is improved survival in times of seasonal famine or when food availability is low.

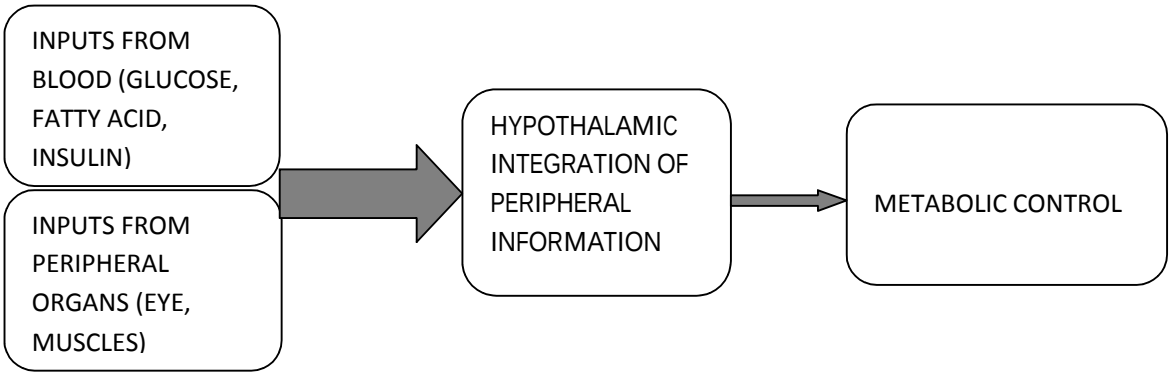
Role of hypothalamus in glycemic control and insulin sensitivity

The hypothalamus (from Greek Hypo = *under* and Thalamus = *room, chamber*) is a portion of the brain that links the nervous system to the endocrine system via the pituitary gland (hypophysis).

The hypothalamus is located below the thalamus, just above the brain stem. It forms the ventral part of the diencephalon. All vertebrate brains contain a hypothalamus.The hypothalamus is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, often called hypothalamic-releasing hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. The hypothalamus controls body temperature, hunger, thirst, fatigue, sleep, and circadian cycles[7].

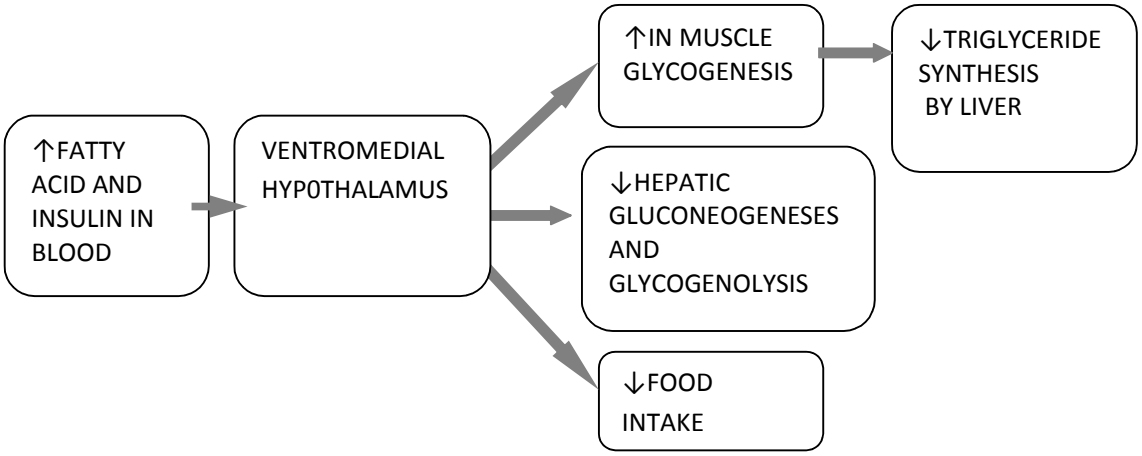
The hypothalamus receives information about changes in the internal and external environment from various inputs, like the neurons of peripheral organs, from the eyes (light) and from the blood (fatty acids, glucose, and hormones). It brings about adjustments to these changes through integration and assessment of the peripheral information that include not only somatic movement but also changes in the rate at which hormones are secreted.

For example circadian rhythms are controlled by subchiasmatic nuclei of hypothalamus by receiving the light information from the eyes. Ventromedial hypothalamic nuclei controls the food intake, regulation of endogenous hepatic gluconeogenesis, and muscle glycogensis are done by receiving the information of glucose, insulin and fatty acids in the blood.



Role of Hypothalamus in metabolism

Ventromedial hypothalamus acts as a glucose sensor. It has multiple connections with other hypothalamic nuclei and plays a pivotal role in modulating autonomic nervous system function, hormonal secretion, peripheral glucose, lipid metabolism, and feeding behavior. Hypothalamic subchiasmatic nucleus oscillates with respect to metabolic signals it receives such as at the time of adequate food intake, it senses the fatty acid and insulin and so it inhibits endogenous glucose production from liver, stimulate glycogen synthesis in muscle and reduces food intake.



Response of Hypothalamus to increased fatty acid and insulin in blood

Role of hypothalamus in diabetes

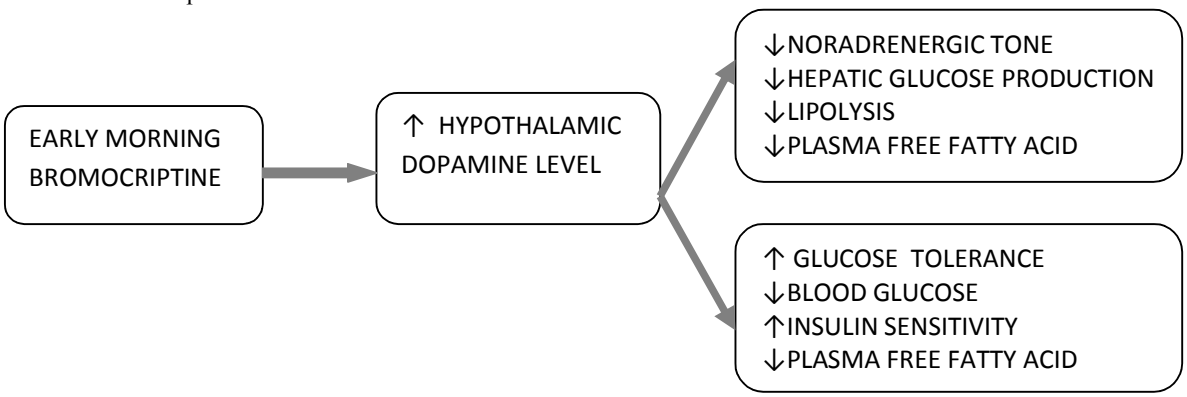
Altered circadian neuroendocrine rhythm affects the glycemic control of the body. Reduction in hypothalamic dopaminergic activity and increased noradrenergic tone play a pivotal role in the development of body fat stores and insulin sensitivity. Reduced dopaminergic tone in the hypothalamus results in excessive glucose production in the liver, and increased peripheral insulin resistance[11-13]. Hypothalamus doesnot respnds to the rise in glucose and lipids after meals and so it doesnot stimulate splanchnic glucose disposal thus the result is hyperglycemia not responding to rise in insulin ie diabetes mellitus.

Proposed mechanism of action of bromocriptine to improve glucose homeostasis and insulin sensitivity

Bromocriptine is a sympatholytic dopamine D2 receptor agonist. It is unique in that it doesnot have a specific receptor that mediates its action on glucose and lipid metabolism[14-17]. Its effects are mediated via resetting of dopaminergic and sympathetic tone within the CNS. Systemic and intracerebral administration of bromocriptine in insulin-resistant animals leads to a decrease in elevated VMH noradrenergic and serotonergic levels with a resultant decline in hepatic glucose production / gluconeogenesis, reduced adipose tissue lipolysis, and improved insulin sensitivity[11-17].Systemic bromocriptine also inhibits VMH responsiveness to norepinephrine, and, conversely, norepinephrine infusion into the VMH antagonizes the beneficial effect of bromocriptine on glucose tolerance and insulin sensitivity. Consistent with these observations in animals, systemic bromocriptine administration improves glycemic control and dyslipidemia without change in body weight in type 2 diabetic and obese nondiabetic humans.

Early morning bromocriptine increases the morning hypothalamic dopamine level, that results in decreased noradrenergic tone, decreased hepatic glucose production, decreased lipolysis and lipogenesis. These factors improves the glucose tolerance, insulin sensitivity and decrease plasma free fatty acid, triglyceride thus improves glycemic control in diabetic patients[7,11-13].

This finding suggests that systemic Bromocriptine alters the monoamine neurotransmitter level within hypothalamic circadian centers and by doing so, they exert significant effects on glucose and lipid metabolism[9].



Effects of early morning bromocriptine

Dose

The recommended dose of bromocriptine is 1.6 mg to 4.8 mg, taken within two hours after waking in the morning18. It should be taken with food to potentially reduce the gastrointestinal side effects such as nausea20-22. Adverse events reported during various clinical trials of bromocriptine included fatigue, nausea, vomiting, dizziness, and headache. These events were more likely to occur during initiation of the treatment and later they were subsided after proper titration of drug. In a 52-week safety clinical trial, bromocritpine mesylate was used at a dosage of 0.8-4.8 mg/day; incidence of nausea was 32.2 % and that of fatigue, vomiting, headache, and dizziness were 13.9, 8.1, 11.4, and 14.8%, respectively18. No dyskinesia was observed during the period of clinical trial18.

Pharmacokinetics

Following ingestion, bromocriptine mesylate tablets are dissolved rapidly and get absorbed within 30 min. When ingested in an empty stomach, the maximum plasma concentration is reached within 60 min[18]. Food delays the absorption and peak plasma levels are reached within 120 min in the fed state. There is extensive hepatic first-pass metabolism by the cytochrome P450 system, specifically CYP3A4. Only 5–10% of the ingested dose reaches the systemic circulation. Ninety-eight percent of ingested bromocriptine is excreted via the biliary route with an elimination half-life of about six hours[18].

Non diabetic uses of bromocriptine

Bromocriptine is used for various fields of medicine like it is used by endocrinologists for the management of pituitary adenomas and hyperprolactinemia, by gynecologists for suppression of lactation, by neurologists in Parkinson's disease and restless legs syndrome, and by cardiologists as a treatment for peripartum cardiomyopathy. In pychiatry it is used for anhedonia in depressed patients[19].

Conclusion

Diabetes mellitus is a chronic metabolic syndrome . It involves multiple organ of the body and leads to various complications. At present a large number of oral hypoglycemic agents and insulin are available for the treatment of type 2 diabetes. There are some recently included drugs like amylin agonist (Pramlintide), analog of glucagon like peptide-1(GLP-1 analog eg. Exenatide and Liraglutide), and inhibitor of dipeptidyl peptidase-4 (DPP-4 inhibitor eg. Sitagliptin).But still there is a need for the development of an antidiabetic agent with minimal side effect and good compliance with different mechanism of action from existing drugs. The traditionally used oral agents are associated with increased risk of adverse events like hypoglycemia, weight gain. lactic acidosis. Also during treatment for long time, their effectiveness decreases due to progressive beta cell failure and later they fail to achieve target glycemic control. So they are used as a combination therapy.

Bromocriptine, used as a novel antidiabetic agents, is a dopamine receptor (D_2) agonist, commonly used for hyperprolactinemia and parkinsonism. Bromocriptine is recently approved for the treatment of type 2 diabetes in addition to diet and exercise. It helps to achieve proper glycemic control. A number of studies carried out have shown that early morning bromocriptine reduces FBS, PPBS and HbA1c level significantly. A study done by Scranton et al. observed the control of hyperglycemia in study subjects with the administration of quick release formulation of bromocriptine. This was also associated with 42% reduction in the episodes of myocardial infarction, stroke, coronary revascularization, and hospitalization in patients suffering from angina or congestive heart failure and a 55% reduction in the episodes of myocardial infarction, stroke, or death. Bromocriptine had shown favourable effects in patients of type 2 diabetes as well as in dyslipidemia. Kamath *et al.* (1997)[15] reported a significant reduction in hyperglycemia and dyslipidemia in obese nondiabetic hyperinsulinemic women. Cincotta *et al.* (1999)[16] observed significant improvement of blood sugar and hyperlipidemia with quick release bromocriptine, administered daily for 6 months. Pijl *et al.* (2000)[14] observed significant reduction in levels

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of both fasting and postprandial (pp) blood glucose level. Aminorroaya *et al*., (2004)[17] administered bromocriptine 2.5 mg daily for 3 months and observed a significant decrease in fasting blood sugar and HbA1c level.

Therefore all these studies demonstrated one thing in common that quick release bromocriptine may prove to be a landmark in the treatment of non-insulin dependent diabetes mellitus. It will be beneficial in obese patients as it takes care of both dyslipidemia as well as hyperglycemia. Thus this drug can be used for its favourable effect to control all the components of the metabolic syndrome. Further, studies are needed to prove its beneficial effect in reduction of body weight in obese diabetics. That will ensure it a preferred agent in obese diabetic patients not responding to conventional oral antidiabetic drugs. Novel mechanism of action, single daily dose, favourable change in lipid profile and lower incidence of cardiovascular events are the points that favors the use of bromocriptine in treatment of type 2 diabetes.

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