

Bromocriptine

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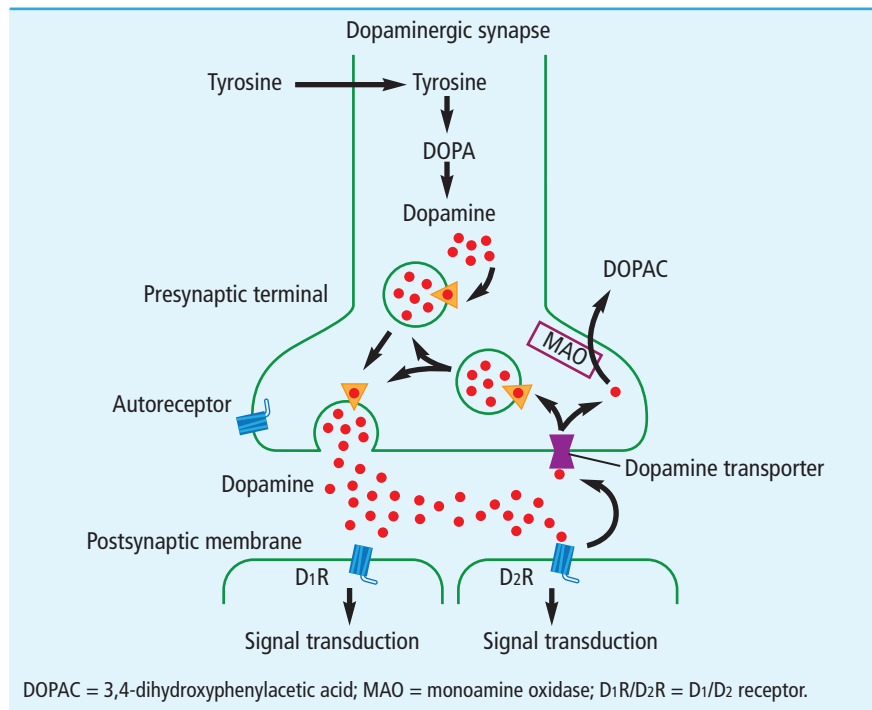


Figure 1. Pharmacological site of action of bromocriptine

Introduction

Bromocriptine (2-bromo- α -ergocriptine) is a potent ergot alkaloid derivative which is an agonist at D₂ dopamine receptors. Ergot alkaloids were first developed in the 1960s and were investigated for their antifertility properties and considered a potential commercial rival to the hormonal contraceptive pill. One of the compounds, CB-154 (later named bromocriptine) was found to have an anti-prolactin effect in animals. It was structurally similar to apomorphine, a known dopaminergic agonist, and was originally trialled and successfully used to treat non-puerperal galactorrhoea. Presently, we have greatest familiarity with its use by endocrinologists in the management of pituitary disease, as well as by neurologists and geriatricians for the treatment of parkinsonism.

Pharmacology

Bromocriptine is a centrally acting agent which directly activates dopamine receptors in the striatum. It is in the same chemical class as the hallucinogen LSD. It is a D₂ agonist and a D₁ antagonist. The specific

effects of D₂ receptor stimulation include inhibition of cyclic AMP production which increases dopamine release and blockade of the D₁ receptor leads to activation of adenylyl cyclase and modulation of D₂ mediated events. It also interacts with various serotonin receptors and it inhibits the release of glutamate, by reversing the GLT-1 transporter.

In 2009, bromocriptine mesylate was approved by the FDA for the treatment of patients with type 2 diabetes (T2DM). It is not currently known what the underlying mechanism of action is for improving glycaemic control. It has been shown to reduce HbA_{1c} by ~0.5%.¹ It has been postulated that it works by inhibiting glucose stimulated insulin secretion by direct activation of the α 2-adrenergic receptors in pancreatic beta cells,² the suggestion being that this 'promotes beta cell rest' through reduction of insulin hypersecretion. However, it may also be through its effects on reducing growth hormone and IGF-1 production directly at the site of the pituitary. Interestingly, many years ago, hypophysectomy used to be considered an efficacious treatment for

advanced diabetic retinopathy and other vascular complications of diabetes, the theory being that removal of pituitary hormones especially ACTH and GH ameliorates the natural progression of poorly controlled diabetes (the Houssay phenomenon of increased insulin sensitivity after hypophysectomy).

The opposite situation of dopamine receptor stimulation may also provide some clues. The relationship between antidopaminergic drugs and glucose has not been extensively studied, but it is recognised that chronic neuroleptic treatment causes hyperinsulinaemia in normal subjects and is associated with diabetes in psychiatric patients.³

The most common side effects of bromocriptine are nausea, vomiting, headache, nasal congestion, fatigue and dizziness. These tend to improve after two to three weeks of therapy and can be minimised by starting with a low dose at night-time and by taking the drug with food. Later side effects include digital vasospasm, constipation, blurring of vision and some neuropsychiatric effects such as confusion and behaviour change. It is contraindicated in patients with syncope, migraine and actually increases the risk of a hypotensive episode in these patients. It is also not advised for use in those with an ergot drug sensitivity and in breastfeeding women as it is likely to inhibit lactation. As is the current concern with cabergoline there is the theoretical risk of fibrotic related complications such as retro-peritoneal fibrosis, pulmonary fibrosis, pleural effusion, pericardial thickening and valvulopathy. Several studies are ongoing or have investigated the potential relationship between bromocriptine exposure and clinically significant cardiac valvulopathy, but no definitive evidence is as yet present for the lower doses that tend to be used in endocrine disease states.

Uses of bromocriptine

In normal individuals, dopamine and dopamine agonists cause an acute rise in circulating growth hormone (GH) levels, probably via hypothalamic mechanisms involving the stimulation of GHRH and inhibition of SRIH release. In acromegaly, for example, dopamine agonists can inhibit GH release through a direct

action on D₂ receptors on the adenomatous somatotroph cells which are not under the normal hypothalamic control. The therapeutic potential of this phenomenon was first demonstrated by Liuzzi et al. in 1972,⁴ and many subsequent studies have documented the actions of bromocriptine in the management of acromegaly as well as other pituitary diseases such as hyperprolactinaemia/prolactinomas where it is known to reduce tumour size. It has also been used to increase sperm counts and restore fertility in oligospermic men without hyperprolactinaemia who are unresponsive to traditional drug therapy.

Bromocriptine is also used in idiopathic Parkinson's disease, usually reserved for cases where levodopa is no longer effective or no longer tolerated. More recently, the non-ergot derived dopamine agonists are preferred due to the reduced risk of fibrotic complications. It can be given to relieve extrapyramidal reactions, hyperthermia, and hypertension of neuroleptic malignant syndrome associated with neuroleptic drug therapy.

Specific evidence for use in diabetes

In the US, bromocriptine is now available as an adjunctive therapy to diet and lifestyle changes in T2DM patients because of its effect on glycaemic control. Although the exact CNS mechanism of action for bromocriptine is unclear, results from preliminary studies suggest that it 'normalises aberrant hypothalamic neurotransmitter activities that induce the insulin resistant, "glucose intolerant" state'.

It has been shown in a 52-week randomised clinical study that once-daily oral bromocriptine administration brings about a significant reduction in postprandial blood glucose values without any increase in plasma insulin.⁵ Approximately 35% of T2DM patients who had 'failed' on other oral hypoglycaemic medications, reached their HbA_{1c} goal after an average of 24 weeks of treatment.⁶ However, it is too early for there to be any data with regard to outcomes. We do not know if there is a long-term reduction in micro- and macrovascular complications of diabetes.

Bromocriptine mesylate is the first drug that has been approved by the FDA since the initiation of new

Key points

- Bromocriptine is a safe, generally well tolerated drug used for a variety of endocrine, neurological and psychiatric disorders
- It has now been approved for use in the context of diabetes; although its exact mechanism of action is unclear, it reduces HbA_{1c} by an average of 0.5%
- There is still concern about the potential risk of fibrotic complications from ergot alkaloid drugs, although the doses used in endocrine disease (and now diabetes) are much less than those used in conditions such as idiopathic Parkinson's disease

guidelines that require studies to demonstrate that diabetes drugs do not increase cardiovascular risk.

Discussion

Bromocriptine appears to have fallen out of favour in recent years: both among endocrinologists as it has been mostly replaced by the longer acting agent cabergoline for prolactin related disorders and by somatostatin analogues for acromegaly, as well as among neurologists who prefer non-ergot derivatives for the management of movement disorders.

It now appears to have taken on a new role for a potentially very large market, that of suppressing hyperglycaemia in the context of diabetes mellitus; although it has a novel pharmacological action different from the plethora of other oral hypoglycaemic agents available, its effect on HbA_{1c} reduction appears rather small. Ultimately, it will be interesting to see if it takes off as a useful therapy and whether regulatory authorities will advise on the use of routine echocardiography in the context of screening for valvular fibrosis in patients taking bromocriptine for diabetes.

Acknowledgments

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Declaration of interests

There are no conflicts of interest declared.

References

References are available online at www.practicaldiabetes.com.

Bromocriptine

References

1. Pijl H, *et al.* Bromocriptine: a novel approach to the treatment of type 2 diabetes. *Diabetes Care* 2000;23:1154–61.
2. De Leeuw Van Weenen JE, *et al.* The dopamine receptor D2 agonist bromocriptine inhibits glucose-stimulated insulin secretion by direct activation of the α 2-adrenergic receptors in beta cells. *Biochem Pharmacol* 2010;79:1827–36.
3. García-Tornadú I, *et al.* Disruption of the dopamine D2 receptor impairs insulin secretion and causes glucose intolerance. *Endocrinology* 2010;151:1441–50.
4. Liuzzi A, *et al.* Inhibitory effect of L-dopa on GH release in acromegalic patients. *J Clin Endocrinol Metab* 1972;35:941–3.
5. Scranton RE, *et al.* A randomised double blind, placebo controlled trial to assess the tolerability and safety during treatment of type 2 diabetes with usual diabetes therapy and either Cycloset or placebo. *BMC Endocr Disord* 2007;7:3.
6. Gaziano JM, *et al.* Randomised clinical trial of quick release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 2010;33:1503–8.