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Invited review

# Dopaminergic drugs in type 2 diabetes and glucose homeostasis

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ABSTRACT

The importance of dopamine in central nervous system function is well known, but its effects on glucose homeostasis and pancreatic β cell function are beginning to be unraveled. Mutant mice lacking dopamine type 2 receptors (D2R) are glucose intolerant and have abnormal insulin secretion. In humans, administration of neuroleptic drugs, which block dopamine receptors, may cause hyperinsulinemia, increased weight gain and glucose intolerance. Conversely, treatment with the dopamine precursor L-DOPA in patients with Parkinson's disease reduces insulin secretion upon oral glucose tolerance test, and bromocriptine improves glycemic control and glucose tolerance in obese type 2 diabetic patients as well as in non diabetic obese animals and humans.

The actions of dopamine on glucose homeostasis and food intake impact both the autonomic nervous system and the endocrine system. Different central actions of the dopamine system may mediate its metabolic effects such as: (i) regulation of hypothalamic noradrenaline output, (ii) participation in appetite control, and (iii) maintenance of the biological clock in the suprachiasmatic nucleus. On the other hand, dopamine inhibits prolactin, which has metabolic functions; and, at the pancreatic beta cell dopamine D2 receptors inhibit insulin secretion.

We review the evidence obtained in animal models and clinical studies that posited dopamine receptors as key elements in glucose homeostasis and ultimately led to the FDA approval of bromocriptine in adults with type 2 diabetes to improve glycemic control. Furthermore, we discuss the metabolic consequences of treatment with neuroleptics which target the D2R, that should be monitored in psychiatric patients to prevent the development in diabetes, weight gain, and hypertriglyceridemia.



**Contents**



*Abbreviations:* AN, arcuate nucleus; D2L, long isoform of the D2R; D2R, dopamine type 2 receptor; D2S, short isoform of the D2R; DOPA, L-3,4-dihydroxyphenylalanine; GH, growth hormone; LacDrd2KO, D2R lactotrope specific knockout; NAc, nucleus accumbens; QR, quick release; SCN, suprachiasmatic nucleus; SN, substantia nigra; ST, striatum; VTA, ventral tegmental area.

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## 1. Introduction

The prevalence of type 2 diabetes is steadily increasing, and has become a pandemic in developed and developing nations [1]. The increased risk of morbidity and mortality and more particularly of atherosclerotic cardiovascular disease associated with type 2 diabetes is of great public health concern.

Previous observational studies focused on the association of glycemic control with all-cause mortality, and most of them showed a positive linear relationship between HbA1c and all-cause mortality [1]. It is clear that improved management of glucose levels and cardiovascular risk factors associated with diabetes are necessary. This review focuses on the role of the dopaminergic system as a new perspective in the control of glucose homeostasis.

The involvement and importance of dopamine as a neurotransmitter and neuromodulator which regulates central nervous system function are well known, but its effect on glucose homeostasis and pancreatic β cell function are not fully deciphered.

Dopamine is one of the major neurotransmitters in the brain which controls a variety of key functions such as locomotion, cognition, feeding behavior, energy homeostasis, motivation, punishment, reward, memory, mood, learning, and hormone secretion. Four major dopamine pathways have been described: the mesocortical pathways (from the ventral tegmental area (VTA) to frontal lobe of prefrontal cortex), mesolimbic pathways (from VTA to nucleus accumbens, *via* hippocampus), and tuberoinfundibular pathway (from the hypothalamus to the pituitary) (Fig. 1).

## 2. Dopamine receptors

Dopamine binds to membrane receptors which belong to the family of seven transmembrane domain G protein-coupled receptors. Five dopamine receptor subtypes have been cloned, and subdivided in D1 and D2-like subfamilies. D1R and DR5 belong to the D1 subfamily coupled to stimulatory G proteins, and D2R–D4R to the D2 subfamily, and are coupled to inhibitory G1/G0 proteins [2]. D2R is expressed in a short (D2S) and a long (D2L) isoform as a result of alternative splicing. Both isoforms bind dopamine with similar affinity, but couple preferentially to different second messengers.

### 2.1. The dopamine type 2 receptor (D2R)

The dopamine type 2 receptor (D2R) is unique in its participation of multifaceted and intertwined processes which target adaptive functions to improve fitness, reproductive success and survival. Many mechanisms which include the selection of nutritious food, or sexual coupling recur to the stimulation of this receptor subtype [3]. D2Rs also participate in motor coordination, locomotion, and several complex behaviors such as executive planning, motivation, aversion and social dominance [4]. The participation of the D2R in the endocrine regulation of prolactin, growth hormone, and insulin, reinforces its role in reproductive success and survival.

#### 2.1.1. Brain dopamine type 2 receptors

In the brain the D2R is located mainly in the basal ganglia, the nucleus accumbens and frontal cortex, participating in locomotor activity, natural reward processing, spatio-temporal organization, and motivation. The substantia nigra pars compacta and the VTA give rise to long dopaminergic fibers, indicating that the D2Rs have a presynaptic location. In contrast, D1-like receptors are exclusively postsynaptic. In the brain the D2R is expressed in the two isoforms, and the long isoform (D2L) is the most abundant.

#### 2.1.2. Pituitary dopamine type 2 receptors

At the pituitary level, D2Rs are expressed in lactotropes, and the long isoform is also preponderant [5].

Dopamine acting on pituitary D2Rs increases potassium conductance and inactivates voltage sensitive $Ca^{2+}$ channels within seconds. As a result the membrane is hyperpolarized, intracellular $Ca^{2+}$ concentration is reduced, and prolactin inhibition ensues. In the absence of dopamine, high intracellular $Ca^{2+}$ concentration is found coupled to high basal prolactin release. Within minutes to hours, dopamine suppresses adenylyl cyclase and inositol phosphate metabolism, leading to decreased prolactin synthesis. And, finally within days, dopamine inhibits lactotrope proliferation [6].

#### 2.1.3. Peripheral dopamine type 2 receptors

Outside the brain the D2R is localized in the retina, kidney, pancreas, and vascular system, besides the pituitary gland. Interestingly, all five dopamine receptor subtypes are expressed in pancreatic β cells [7], and the pancreatic D2R is inhibitory to glucose stimulated insulin secretion in isolated islets from rodents [8] as well as in β cell lines [7].

## 3. The D2R and glucose homeostasis

Since 1980 it has been documented that the dopamine agonist bromocriptine exerts an inhibitory effect on hyperglycemia in people with type 2 diabetes [9]. Increasing evidence in later years posited dopamine receptors as key elements in glucose homeostasis, which ultimately led to the FDA approval of bromocriptine for use "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes".

In humans, administration of neuroleptic drugs, which block dopamine receptors, causes hyperinsulinemia in normal subjects [10], or is associated with diabetes in psychiatric patients [11–14]. Both for atypical and typical antipsychotics the adverse effects of