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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

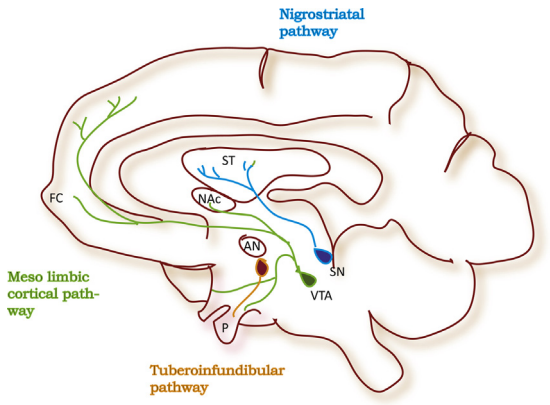

Fig. 1. Dopaminergic pathways in the brain. AN: arcuate nucleus, FC: frontal cortex, NAc; nucleus accumbens, SN: substancia nigra, ST: striatum, VTA: ventral tegmental area.

weight gain and impaired glucose tolerance have been described [15,16]. Furthermore, it was described that central dopaminergic activity is inversely correlated with BMI, glycated hemoglobin and insulin resistance [17].

Conversely, treatment with the dopamine precursor L-DOPA in patients with Parkinson's disease reduces insulin secretion upon an oral glucose tolerance test [18]. It has also been shown that bromocriptine improves glycemic control and glucose tolerance in obese type 2 diabetic patients [19] as well as in non diabetic obese animals and humans. Bromocriptine can reverse many of the metabolic alterations associated with obesity.

In rodents it has been described that L-DOPA administration increases pancreatic content of dopamine (in β cells) [20,21] and consequently decreases insulin secretion induced by secretagogues. Furthermore, dopamine antagonists in male rats evoked high glucose and insulin levels [22,66]. These results suggest that even though insulin secretion is mainly regulated by glucose, it can be fine tuned by parasympathtetic or sympathetic input, and particularly by the dopaminergic system [23].

Furthermore, some *in vitro* studies performed in isolated pancreatic islets point to the participation of the pancreatic D2R in insulin secretion, and beta cell proliferation and apoptosis [7,8,24–28]. And, siRNA-mediated knockdown of D2Rs, but not other dopamine receptor subtypes, affects glucose-stimulated insulin secretion in β cell lines, such as insulin-secreting INS-1E cells [29].

4. Mechanism of action of D2R activation on glucose homeostasis

Dopaminergic agents exert central as well as peripheral actions which modulate glucose and energy homeostasis. These actions impact both the autonomic nervous system and the endocrine system (Fig. 2).

4.1. Central nervous system

Different central actions of the dopamine system may mediate its effects on metabolic regulation: (i) regulation of hypothalamic noradrenaline output, (ii) participation in appetite control, and (iii) maintenance of the biological clock in the suprachiasmatic nucleus.

4.1.1. Regulation of hypothalamic noradrenaline output

It is well documented that elevations of noradrenaline in the hypothalamus lead to hyperglycemia, high plasma free fatty acid levels, increased appetite, and obesity [30,31]. Activation of D2Rs reduces the secretion of noradrenaline, and therefore dopamine agonists may have beneficial effects on metabolism through suppression of the sympathetic nervous system [32]. In fact, it has been suggested that the effect of dopamine timed release evokes metabolic changes such as insulin sensitization, by modifying cerebral signals, which ultimately decrease elevated serotonin and noradrenaline activity [33].

4.1.2. Participation in appetite control

Central dopaminergic 'reward' pathways contribute to appetite control in combination with the classic system of energy homeostasis. Especially, dopaminergic projections from the VTA to the nucleus accumbens have been linked to drug addiction [34]. Humans with decreased central D2Rs are more vulnerable to compulsive behaviors, including food intake; and decreased D2Rs associate with addiction to food or drugs [34,35]. To this regard severely obese individuals have shown defective dopamine neurotransmission with decreased striatal D2R availability [36], which suggests a neuroadaptive response to overconsumption of palatable food.

Even though data studying the relation of D2R gene mutations and obesity in humans is still limited, most evidence points to an association of overweight with loss of function mutations [11,37,38].

From the opposite state of obesity, it has been described that patients suffering from anorexia nervosa have increased striatal D2R levels, and recent studies have revealed an association between anorexia nervosa and multiple D2R polymorphisms [39]. In addition, increased striatal D2R density was observed after weight loss following bariatric surgery (gastric bypass) in obese patients [40]. And finally, it has been suggested that treatment with dopamine agonists could improve the treatment of obesity [41].

In rodents decreased striatal and hypothalamic activity of dopamine receptors leads to a compensatory hyperphagia and excess weight gain [42]. Therefore, abundant data in humans and rodents point to the dopaminergic system as a key factor regulating food intake, and overeating is generally associated with obesity and altered glucose metabolism.

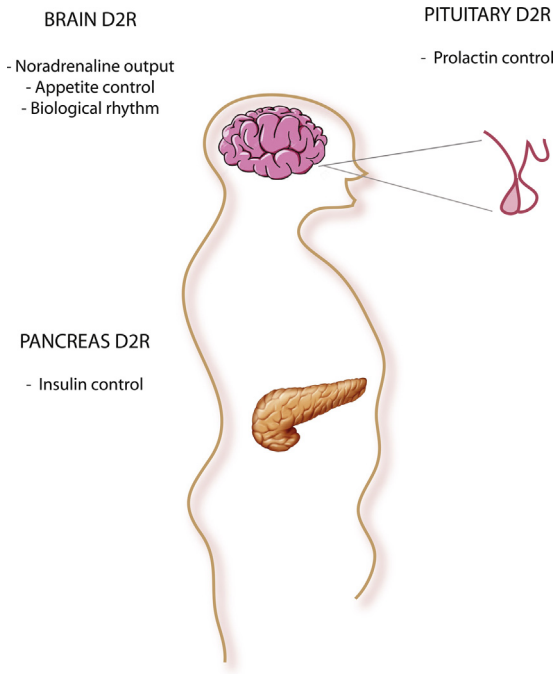

Fig. 2. Possible sites of D2R participation in the regulation of glucose homeostasis.

4.1.3. Maintenance of the biological clock in the suprachiasmatic nucleus

It has been described that in healthy individuals there is an early morning peak in hypothalamic dopaminergic activity [43]. This observation was the basis for the use of bromocriptine within 2 h of waking, to mimic and resynchronize the natural dopaminergic circadian rhythm which may be faulty in diabetic patients.

In fact, the circadian rhythm of dopamine release at the region of the biological clock, namely the hypothalamic suprachiasmatic nuclei (SCN), has been implicated in the regulation of peripheral insulin sensitivity as well as in glucose and lipid metabolism in seasonal mammals [43]. This circadian rhythm of dopamine release at the SCN is absent in seasonal insulin resistant animals [44], and disruption of this dopaminergic activity by SCN site-specific neurotoxin application in both seasonal and non-seasonal insulin sensitive animals induces a marked insulin resistant state [33].

Moreover, intraperitoneal or intracerebroventricular administration of bromocriptine to seasonal insulin resistant animals reverses the insulin resistance or glucose intolerance [45,46]. Such bromocriptine treatment reduces both hepatic glucose and lipid production and secretion [46–48].

4.2. Pancreas

Dopamine agents may improve metabolic outcome acting directly at the pancreatic level. Dopamine acting on β cells might originate in neurons innervating pancreatic islets, the exocrine pancreas [49], or the endocrine pancreas itself [27]. The link between the central nervous system and the pancreatic islets has been well established. The hypothalamic paraventricular nucleus has direct connections with the dorsal vagal complex [50], and the central vagal connection with dopaminergic innervations is reported to reach the pancreatic islets through the parahypothalamic ventricular nucleus [51].

D2Rs are expressed in pancreatic β cells and mediate an inhibition of insulin secretion [7,8]. With regard to the mechanism of action at this level, it is well known that glucose-induced electrical activity of β-cells leads to the opening of voltage-gated Ca^{2+} channels with subsequent Ca^{2+} influx, and Ca^{2+} dependent exocytosis of insulin [52]. Dopamine decreases cell membrane depolarization as well as cytosolic Ca^{2+} entry, decreasing insulin secretion evoked by glucose [7].

Furthermore, it has been reported that dopamine has an antiincretin, antiproliferative effect on pancreatic β cells [27,53].

4.3. Pituitary

At the pituitary level dopamine agents may have an indirect effect on glucose homeostasis through the regulation of pituitary hormones.

Lactotrope D2Rs inhibit prolactin synthesis and release, as well as lactotrope proliferation, and prolactin has been considered a metabolic hormone involved in food intake and lipid accretion [54]. From a biological perspective, prolactin may be a major factor mediating the hyperphagia in pregnancy and lactation [55,56]. In particular, high prolactin levels observed in pregnant and lactating females may contribute to a hyperphagic state [55] probably sustained by leptin resistant hypothalamic centers controling food intake [57]. Prolactin has been linked to body weight gain and increased adiposity in lactotrope specific D2R knockout mice [58]. Therefore. dopamine agents which lower serum prolactin might prevent the hyperphagic and lipogenic action of this hormone.

Furthermore, in acromegalic patients, activation of D2Rs decreases GH release [59,60]. Therefore, improvement of glucose tolerance by dopamine may be related to suppression of GH secretion, and the consequent inhibition of GH-mediated antagonism of insulin action.

5. Preclinical animal studies

Several preclinical studies demonstrated that administration of bromocriptine to diabetic or obese animal models improved glucose intolerance, reduced high insulin and lipid levels in serum [32,48,61–63]. It was suggested that bromocriptine action is related, at least in part, to its capacity of modifying hypothalamic dopamine circadian rhythm (see Section 4.1.3) [33,63]. Animal studies provided evidence that the timing of bromocriptine administration, early after light onset, is critical to obtain adequate results in glucose homeostasis [64]. In this regard, it was demonstrated that bromocriptine resets corticosteroid rhythms, and the effect may last for weeks after withdrawal of treatment, suggesting that the adjustment in the biological clock is not temporary [65]. Furthermore, in SHR with metabolic syndrome bromocriptine impacted on liver metabolism potentiating a reduction of elevated lipogenic and gluconeogenic capacity [63].

On the other hand, male rats treated with sulpiride, which is a dopamine antagonist, exhibit high insulin and high glucose levels [22,66], and atypical antipsychotics acutely induce side metabolic effects in rats [66]. In D2R knockout mice, a transgenic tool which mimics chronic antidopaminergic treatments, impaired insulin response, high fasting glucose, and glucose intolerance were noted, indicating a fundamental role of D2Rs in glucose homeostasis [8]. Glucose intolerance resulted from a blunted insulin secretory response, rather than insulin resistance, as shown by impaired glucose stimulated insulin secretion *in vivo* and *in vitro,* and a conserved insulin tolerance test *in vivo*. Furthermore, short term treatment with cabergoline, a dopamine agonist, led to decreased insulin response and consequent glucose intolerance in wildtype, but not in D2R knockout mice, pointing to an inhibitory role of D2Rs on insulin release. This effect was partly offset by haloperidol, a dopamine antagonist at D2R [8] and was also verified in isolated islets *in vitro* indicating a role for pancreatic D2Rs. At later stages of development a reduced β cell mass was observed in D2R knockout mice.

Therefore, studies with this transgenic knockout model demonstrate that pancreatic D2Rs inhibit glucose-stimulated insulin release, but chronic failure of dopaminergic inhibition throughout development may exert a gradual deteriorating effect on insulin homeostasis, so that eventually reduced β cell mass and glucose intolerance develop.

Recent studies using conditional mutant female mice lacking D2Rs in pituitary lactotropes (lacDrd2KO) also point to an indirect role of dopamine on glucose homeostasis. These mice have intact pancreatic and central D2Rs, but display chronic hyperprolactinemia and lactotrope hyperplasia. As a result, increased food intake, marked body weight gain and adipose tissue accretion, as well as glucose intolerance develop [58]. These results highlight the hyperphagic and lipogenic effects of chronically elevated prolactin levels due to disruption of lactotrope D2Rs, which are better evidenced in the presence of functional central D2Rs.

Increased adiposity has been linked to insulin resistance [67], but even though lacDrd2KO mice had glucose intolerance, and decreased insulin response to glucose overload, insulin resistance was not clearly evidenced [58]. This may be indicative of a defective insulin secretion at the level of the pancreatic β cell. Intolerance to glucose is observed in chronic hyperprolactinemic pituitary-grafted rats [68], but also in prolactin receptor-deficient mice [69], highlighting the complex and unresolved participation of prolactin in carbohydrate metabolism [70].

6. Metabolic changes associated to antidopaminergic medications in severe mental illness

Most antipsychotics have D2R antagonist activity with varying degrees of potency. They are used in psychiatry to treat major psychiatric disorders, including schizophrenia, psychotic depression and bipolar disorder, disorders linked to dopaminergic dysfunction.

Following the introduction of antipsychotic medications into the clinical practice, a number of reports suggested that treatment with these agents is associated with an increase in obesity, clinical presentation of new onset diabetes mellitus or diabetic ketoacidosis, and the development of hypertriglyceridemia [71–74].

Furthermore, it was also documented that chronic treatment with antipsychotic medications in humans, which can induce abnormalities in glucose metabolism, may increase the risk not only for diabetes but for cardiovascular disease [15,75–77]. And importantly, it was reported that older diabetics who take antipsychotic medications have an increased risk of ending up in the hospital with elevated blood glucose levels, or hyperglycemia [78].

It is imperative that psychiatrists bear in mind the possible metabolic consequences of medications. Regular metabolic monitoring of patients could alert to the development of diabetes and hypertriglyceridemia in patients on chronic antipsychotics which target the dopamine system.

7. Metabolic changes associated to dopamine agonist treatment in Parkinson's disease, acromegaly and prolactinomas

Conversely, dopaminergic treatment of Parkinson's disease, prolactinomas or acromegaly has been linked to improvement of glucose tolerance.

For example, treatment with the dopamine precursor L-DOPA in patients with Parkinson's disease reduces insulin secretion upon oral glucose tolerance test [18].

In patients with acromegaly, bromocriptine treatment improved glucose tolerance by suppressing GH secretion from the pituitary adenomas, and thus suppressing the GH-mediated antagonism of insulin action [79].

It has also been suggested that the effect of bromocriptine on blood glucose and improvement of glucose tolerance in maturity onset diabetics is due its prolactin lowering action [9]. Sustained elevation of prolactin levels, as in the case of prolactinomas, has been associated with increased body weight; and normalization of prolactin levels with dopamine agonists decreased body weight gain [80]. Therefore, because an increase in body weight and adiposity are associated to metabolic changes, prolactin which is regulated by dopamine pathways remains a plausible link between dopamine and metabolic regulation.

8. *D2R* gene polymorphisms and glucose homeostasis in humans

D2R gene polymorphisms have been studied in association with cognition, smoking addiction, alcohol dependence or depression [81], but few reports deal with the relations between D2R variants and glucose homeostasis or type 2 diabetes.

A recent study evaluated the relationship between *D2R* polymorphisms, glucose-stimulated insulin secretion and type 2 diabetes in a cohort of 25,000 people (8148 with type 2 diabetes and 17,687 control subjects) [82]. In this study, the rs1800497 single nucleotide polymorphism at the Drd2/ANKK1 locus was associated with a significantly increased risk for type 2 diabetes in women but not in men, and a single nucleotide polymorphism at the rs6275 locus in the *D2R* gene was associated with increased first-phase glucose-stimulated insulin secretion, also in women only, identifying potential sex-specific type 2 diabetes susceptibility genes linked to the D2R [82].

Interestingly, in severe mental illness the rate of diabetes mellitus is increased by two to three fold [83]; and these disorders are related to alterations in dopamine pathways. Areas in the genome which may determine the risk of severe mental illness overlap with areas associated with diabetes or metabolic disorders, in particular the 1q21-42 32 region [84]. Furthermore, Genome-wide association studies determined that both schizophrenia and type 2 diabetes are highly heritable disorders. Many of the genes associated with schizophrenia are expressed in the brain, and include the gene that encodes the *D2R* [85,86].

Various polymorphisms in genes related to insulin resistance, adipogenesis or β cell function and mass have been described [82], and at least 37 have been identified as risk genes both for type 2 diabetes and schizophrenia [82]. Importantly, the D2R was proposed to participate in the development of obesity and type 2 diabetes, modifying insulin secretion and sensitivity [87], as well as in the risk of schizophrenia [85].

Another gene that has been associated with both insulin resistance and schizophrenia is the tyrosine hydroxylase gene, fundamental in the pathway of dopamine synthesis. Polymorphisms in this gene have been pointed in the development of diabetes mellitus in people with severe mental illness [86,88].

9. Clinical benefits of bromocriptine in type 2 diabetes

Bromocriptine became the first dopaminergic drug approved and patented to be used in type 2 diabetes [89], after demonstration of innocuity in cardiovascular the system.

Soon, different preparations which provide quick release (QR), or high absorbation have been patented [90–92].

Various studies were previously undertaken to evaluate the effect of bromocriptine on weight and glycemia in obese non-diabetic and diabetic individuals, and marked reductions in fasting plasma glucose levels were found. In addition, weight loss, body fat loss and improved glucose tolerance was also reported in clinical trials in obese men [92,93].

Cardiovascular safety was demonstrated in a large 52 weeks long study (the Cylcoset trial) involving 3095 patients with type 2 diabetes treated with bromocriptine QR. The treated group reported less serious adverse effects and cardiovascular disease end points [94].

Bromocriptine also presents a beneficial effect on plasma lipids probably secondary to the activation of central nervous system dopaminergic pathways [32]. It significantly reduces both lipolysis and lipogenesis but as the reduction is greater for lipogenesis the net effect is to promote fat mobilization and reduce fat stores [95].

As stated, administration of bromocriptine-QR within 2 h of waking aims at replicating the normal early peak in dopaminergic activity so as to resynchronize the circadian rhythms to those of healthy individuals. The drug can be combined with both metformin and sulphonylureas. Common adverse effects found in clinical trials were nausea, and vomiting, which were for the most part transient and modest to moderate in severity [96]. No severe hypoglycemia was reported, and there was no increased risk for hypotension in the bromocriptine-QR group.

Finally, even though some data suggested that bromocriptine may have a protective effect on the preservation of endogenous insulin secretory capacity of β cells [97], it is not recommended for use in type 1 diabetes.

10. Conclusions

In the last 30 years, accumulating evidence has posited the dopamine system as an important player in glucose homeostasis control. Preclinical data obtained in rodents using antidopaminergic agents, as well as in D2R knockout models showed increments in glucose and insulin levels. Data obtained from *in vitro* and *in vivo* studies determined that dopamine acting on the D2R modifies glucose and insulin levels acting at different levels: central nervous system, pituitary and pancreas. Preclinical and clinical studies were paramount in FDA approval of bromocriptine in type 2 diabetes. These same studies should alert to the undesired effects of chronic treatments with neuroleptics which target the D2R, and may have important metabolic consequences in patients.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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References

[1] W. Li, P.T. Katzmarzyk, R. Horswell, Y. Wang, J. Johnson, G. Hu, HbA1c and all-cause mortality risk among patients with type 2 diabetes, Int. J. Cardiol. 202 (2016) 490–496.
[2] C. Missale, S.R. Nash, S.W. Robinson, M. Jaber, M.G. Caron, Dopamine receptors: from structure to function, Physiol. Rev. 78 (1998) 189–225.
[3] I. Garcia-Tornadu, M.I. Perez-Millan, V. Recouvreux, M.C. Ramirez, G. Luque, G.S. Risso, et al., New insights into the endocrine and metabolic roles of dopamine D2 receptors gained from the Drd2 mouse, Neuroendocrinology 92 (2010) 207–214.
[4] D. Noain, M.I. Perez-Millan, E.P. Bello, G.M. Luque, C.R. Casas, D.M. Gelman, et al., Central dopamine D2 receptors regulate growth-hormone-dependent body growth and pheromone signaling to conspecific males, J. Neurosci. 33 (2013) 5834–5842.
[5] D. Guivarc'h, P. Vernier, J.D. Vincent, Sex steroid hormones change the differential distribution of the isoforms of the D2 dopamine receptor messenger RNA in the rat brain, Neuroscience 69 (1995) 159–166.
[6] N. Ben Jonathan, R. Hnasko, Dopamine as a prolactin (PRL) inhibitor, Endocr. Rev. 22 (2001) 724–763.
[7] B. Rubi, S. Ljubicic, S. Pournourmohammadi, S. Carobbio, M. Armanet, C. Bartley, et al., Dopamine D2-like receptors are expressed in pancreatic beta cells and mediate inhibition of insulin secretion, J. Biol. Chem. 280 (2005) 36824–36832.
[8] I. Garcia-Tornadu, A.M. Ornstein, A. Chamson-Reig, M.B. Wheeler, D.J. Hill, E. Arany, et al., Disruption of the dopamine D2 receptor impairs insulin secretion and causes glucose intolerance, Endocrinology 151 (2010) 1441–1450.
[9] A.H. Barnett, C. Chapman, K. Gailer, C.J. Hayter, Effect of bromocriptine on maturity onset diabetes, Postgrad. Med. J. 56 (1980) 11–14.
[10] M.O. Sowell, N. Mukhopadhyay, P. Cavazzoni, S. Shankar, H.O. Steinberg, A. Breier, et al., Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo, J. Clin. Endocrinol. Metab. 87 (2002) 2918–2923.
[11] H. Pijl, Reduced dopaminergic tone in hypothalamic neural circuits: expression of a thrifty genotype underlying the metabolic syndrome? Eur. J. Pharmacol. 480 (2003) 125–131.
[12] L. Citrome, A. Jaffe, J. Levine, B. Allingham, J. Robinson, Relationship between antipsychotic medication treatment and new cases of diabetes among psychiatric inpatients, Psychiatr. Serv. 55 (2004) 1006–1013.
[13] S.R. Marder, S.M. Essock, A.L. Miller, R.W. Buchanan, D.E. Casey, J.M. Davis, et al., Physical health monitoring of patients with schizophrenia, Am. J. Psychiatry 161 (2004) 1334–1349.
[14] M. De Hert, J. Detraux, R. van Winkel, W. Yu, C.U. Correll, Metabolic and cardiovascular adverse effects associated with antipsychotic drugs, Nat. Rev. Endocrinol. 8 (2012) 114–126.
[15] H.E. Lebovitz, Metabolic consequences of atypical antipsychotic drugs, Psychiatr. Q. 74 (2003) 277–290.
[16] J.E. de Leeuw van Weenen, E.T. Parlevliet, J.P. Schroder-van der Elst, S.A. van den Berg, K. Willems van Dijk, J.A. Romijn, et al., Pharmacological modulation of dopamine receptor D2-mediated transmission alters the metabolic phenotype of diet induced obese and diet resistant C57Bl6 mice, Exp. Diabetes Res. 2011 (2011) 928523.
[17] L. Brunerova, J. Potockova, J. Horacek, J. Suchy, M. Andel, Central dopaminergic activity influences metabolic parameters in healthy men, Neuroendocrinology 97 (2013) 132–138.
[18] G. Rosati, M. Maioli, I. Aiello, A. Farris, V. Agnetti, Effects of long-term L-DOPA therapy on carbohydrate metabolism in patients with Parkinson's disease, Eur. Neurol. 14 (1976) 229–239.
[19] H. Pijl, S. Ohashi, M. Matsuda, Y. Miyazaki, A. Mahankali, V. Kumar, et al., Bromocriptine: a novel approach to the treatment of type 2 diabetes, Diabetes Care 23 (2000) 1154–1161.
[20] L.E. Ericson, R. Hakanson, I. Lundquist, Accumulation of dopamine in mouse pancreatic B-cells following injection of l-DOPA. Localization to secretory granules and inhibition of insulin secretion, Diabetologia 13 (1977) 117–124.
[21] R.T. Zern, J.L. Bird, J.M. Feldman, Effect of increased pancreatic islet norepinephrine, dopamine and serotonin concentration on insulin secretion in the golden hamster, Diabetologia 18 (1980) 341–346.
[22] T. Baptista, A. Lacruz, X. Paez, L. Hernandez, S. Beaulieu, The antipsychotic drug sulpiride does not affect bodyweight in male rats. Is insulin resistance involved? Eur. J. Pharmacol. 447 (2002) 91–98.
[23] B. Ahren, Autonomic regulation of islet hormone secretion—implications for health and disease, Diabetologia 43 (2000) 393–410.
[24] M.J. Garcia Barrado, M.C. Iglesias Osma, E.J. Blanco, H.M. Carretero, R.V. Sanchez, I.L. Catalano, et al., Dopamine modulates insulin release and is involved in the survival of rat pancreatic beta cells, PLoS One 10 (2015) e0123197.
[25] C.R. Nogueira, U.F. Machado, R. Curi, A.R. Carpinelli, Modulation of insulin secretion and $^{45}Ca^{2+}$ efflux by dopamine in glucose-stimulated pancreatic islets, Gen. Pharmacol. 25 (1994) 909–916.
[26] E. Shankar, K.T. Santhosh, C.S. Paulose, Dopaminergic regulation of glucose-induced insulin secretion through dopamine D2 receptors in the pancreatic islets in vitro, IUBMB Life 58 (2006) 157–163.
[27] A. Ustione, D.W. Piston, P.E. Harris, Minireview dopaminergic regulation of insulin secretion from the pancreatic islet, Mol. Endocrinol. 27 (2013) 1198–1207.
[28] E.S. Di Cairano, S. Moretti, P. Marciani, V.F. Sacchi, M. Castagna, A. Davalli, et al., Neurotransmitters and neuropeptides: new players in the control of islet of Langerhans' cell mass and function, J. Cell. Physiol. 231 (2016) 756–767.
[29] W. Wu, J. Shang, Y. Feng, C.M. Thompson, S. Horwitz, J.R. Thompson, et al., Identification of glucose-dependant insulin secretion targets in pancreatic beta cells by combining defined-mechanism compound library screening and siRNA gene silencing, J. Biomol. Screen. 13 (2008) 128–134.
[30] T. Shimazu, M. Noma, M. Saito, Chronic infusion of norepinephrine into the ventromedial hypothalamus induces obesity in rats, Brain Res. 369 (1986) 215–223.
[31] G.A. Smythe, H.S. Grunstein, J.E. Bradshaw, M.V. Nicholson, P.J. Compton, Relationships between brain noradrenergic activity and blood glucose, Nature 308 (1984) 65–67.
[32] S. Luo, A.H. Meier, A.H. Cincotta, Bromocriptine reduces obesity, glucose intolerance and extracellular monoamine metabolite levels in the ventromedial hypothalamus of Syrian hamsters, Neuroendocrinology 68 (1998) 1–10.
[33] S. Luo, J. Luo, A.H. Meier, A.H. Cincotta, Dopaminergic neurotoxin administration to the area of the suprachiasmatic nuclei induces insulin resistance, Neuroreport 8 (1997) 3495–3499.
[34] R.D. Palmiter, Is dopamine a physiologically relevant mediator of feeding behavior? Trends Neurosci. 30 (2007) 375–381.
[35] J.H. Baik, Dopamine signaling in food addiction: role of dopamine D2 receptors, BMB Rep. 46 (2013) 519–526.
[36] G.J. Wang, N.D. Volkow, J. Logan, N.R. Pappas, C.T. Wong, W. Zhu, et al., Brain dopamine and obesity, Lancet 357 (2001) 354–357.
[37] S.O. Fetissov, M.M. Meguid, On dopamine, D2 receptor, and Taq1A polymorphism in obesity and anorexia, Nutrition 25 (2009) 132–133.
[38] C.L. Roth, A. Hinney, E.A. Schur, C.T. Elfers, T. Reinehr, Association analyses for dopamine receptor gene polymorphisms and weight status in a longitudinal analysis in obese children before and after lifestyle intervention, BMC Pediatr. 13 (2013) 197.
[39] A.W. Bergen, M. Yeager, R.A. Welch, K. Haque, J.K. Ganjei, M.B. van den Bree, et al., Association of multiple DRD2 polymorphisms with anorexia nervosa, Neuropsychopharmacology 30 (2005) 1703–1710.
[40] K.E. Steele, G.P. Prokopowicz, M.A. Schweitzer, T.H. Magunsuon, A.O. Lidor, H. Kuwabawa, et al., Alterations of central dopamine receptors before and after gastric bypass surgery, Obes. Surg. 20 (2010) 369–374.
[41] A.H. Meier, A.H. Cincotta, W.C. Lovell, Timed bromocriptine administration reduces body fat stores in obese subjects and hyperglycemia in type II diabetics, Experientia 48 (1992) 248–253.
[42] P.M. Johnson, P.J. Kenny, Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats, Nat. Neurosci. 13 (2010) 635–641.

[43] A.H. Meier, A.H. Cincotta, Circadian rhythms regulate the expression of the thrifty genotype/phenotype, Diabetes Rev. 4 (1996) 464–487.
[44] S. Luo, J. Luo, A.H. Cincotta, Suprachiasmatic nuclei monoamine metabolism of glucose tolerant *versus* intolerant hamsters, Neuroreport 10 (1999) 2073–2077.
[45] A.H. Cincotta, T.A. MacEachern, A.H. Meier, Bromocriptine redirects metabolism and prevents seasonal onset of obese hyperinsulinemic state in Syrian hamsters, Am. J. Physiol. 264 (1993) E285–E293.
[46] A.H. Cincotta, B.C. Schiller, A.H. Meier, Bromocriptine inhibits the seasonally occurring obesity, hyperinsulinemia, insulin resistance, and impaired glucose tolerance in the Syrian hamster, *Mesocricetus auratus*, Metabolism 40 (1991) 639–644.
[47] A.H. Cincotta, A.H. Meier, Prolactin permits the expression of a circadian variation in lipogenic responsiveness to insulin in hepatocytes of the golden hamster (*Mesocricetus auratus*), J. Endocrinol. 106 (1985) 173–176.
[48] A.H. Cincotta, A.H. Meier, Bromocriptine inhibits *in vivo* free fatty acid oxidation and hepatic glucose output in seasonally obese hamsters (*Mesocricetus auratus*), Metabolism 44 (1995) 1349–1355.
[49] E. Mezey, G. Eisenhofer, G. Harta, S. Hansson, L. Gould, B. Hunyady, et al., A novel nonneuronal catecholaminergic system: exocrine pancreas synthesizes and releases dopamine, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 10377–10382.
[50] L.W. Swanson, P.E. Sawchenko, Paraventricular nucleus: a site for the integration of neuroendocrine and autonomic mechanisms, Neuroendocrinology 31 (1980) 410–417.
[51] B.J. Davis, P.H. Smith, Effects of substantia nigra lesions on the volumes of A, B, and D cells and the content of insulin and glucagon in the rat pancreas, Diabetologia 28 (1985) 756–762.
[52] J. Lang, Molecular mechanisms and regulation of insulin exocytosis as a paradigm of endocrine secretion, Eur. J. Biochem. 259 (1999) 3–17.
[53] A. Maffei, A.M. Segal, J.C. Alvarez-Perez, A. Garcia-Ocana, P.E. Harris, Anti-incretin, anti-proliferative action of dopamine on beta-cells, Mol. Endocrinol. 29 (2015) 542–557.
[54] N. Ben Jonathan, E. Hugo, Prolactin (PRL) in adipose tissue: regulation and functions, Adv. Exp. Med. Biol. 846 (2015) 1–35.
[55] B. Woodside, Prolactin and the hyperphagia of lactation, Physiol. Behav. 91 (2007) 375–382.
[56] M.C. Garcia, M. Lopez, O. Gualillo, L.M. Seoane, C. Dieguez, R.M. Senaris, Hypothalamic levels of NPY, MCH, and prepro-orexin mRNA during pregnancy and lactation in the rat: role of prolactin, FASEB J. 17 (2003) 1392–1400.
[57] L. Naef, B. Woodside, Prolactin/leptin interactions in the control of food intake in rats, Endocrinology 148 (2007) 5977–5983.
[58] M.I. Perez Millan, G.M. Luque, M.C. Ramirez, D. Noain, A.M. Ornstein, M. Rubinstein, et al., Selective disruption of dopamine D2 receptors in pituitary lactotropes increases body weight and adiposity in female mice, Endocrinology 155 (2014) 829–839.
[59] U.A. White, J.M. Stephens, Transcriptional factors that promote formation of white adipose tissue, Mol. Cell. Endocrinol. 318 (2010) 10–14.
[60] C.A. Jaffe, A.L. Barkan, Treatment of acromegaly with dopamine agonists, Endocrinol. Metab. Clin. N. Am. 21 (1992) 713–735.
[61] S. Luo, J. Luo, A.H. Cincotta, Association of the antidiabetic effects of bromocriptine with a shift in the daily rhythm of monoamine metabolism within the suprachiasmatic nuclei of the Syrian hamster, Chronobiol. Int. 17 (2000) 155–172.
[62] S. Luo, Y. Liang, A.H. Cincotta, Intracerebroventricular administration of bromocriptine ameliorates the insulin-resistant/glucose-intolerant state in hamsters, Neuroendocrinology 69 (1999) 160–166.
[63] M. Ezrokhi, S. Luo, Y. Trubitsyna, A.H. Cincotta, Neuroendocrine and metabolic components of dopamine agonist amelioration of metabolic syndrome in SHR rats, Diabetol. Metab. Syndr. 6 (2014) 104.
[64] A.H. Cincotta, A.H. Meier, J.M. Cincotta, Bromocriptine improves glycaemic control and serum lipid profile in obese type 2 diabetic subjects: a new approach in the treatment of diabetes, Expert Opin. Investig. Drugs 8 (1999) 1683–1707.
[65] A.H. Cincotta, A.H. Meier, L.L. Southern, Bromocriptine alters hormone rhythms and lipid metabolism in swine, Ann. Nutr. Metab. 33 (1989) 305–314.
[66] A.F. Chintoh, S.W. Mann, L. Lam, A. Giacca, P. Fletcher, J. Nobrega, et al., Insulin resistance and secretion in vivo: effects of different antipsychotics in an animal model, Schizophr. Res. 108 (2009) 127–133.
[67] S.E. Kahn, R.L. Hull, K.M. Utzschneider, Mechanisms linking obesity to insulin resistance and type 2 diabetes, Nature 444 (2006) 840–846.
[68] F.M. Reis, A.M. Reis, C.C. Coimbra, Effects of hyperprolactinaemia on glucose tolerance and insulin release in male and female rats, J. Endocrinol. 153 (1997) 423–428.
[69] M. Freemark, I. Avril, D. Fleenor, P. Driscoll, A. Petro, E. Opara, et al., Targeted deletion of the PRL receptor: effects on islet development, insulin production, and glucose tolerance, Endocrinology 143 (2002) 1378–1385.
[70] R.S. Brown, A.E. Herbison, D.R. Grattan, Effects of prolactin and lactation on A15 dopamine neurones in the rostral preoptic area of female mice, J. Neuroendocrinol. 27 (2015) 708–717.
[71] L.E. Rojo, P.A. Gaspar, H. Silva, L. Risco, P. Arena, K. Cubillos-Robles, et al., Metabolic syndrome and obesity among users of second generation antipsychotics: a global challenge for modern psychopharmacology, Pharmacol. Res. 101 (2015) 74–85.
[72] D.C. Henderson, P.M. Doraiswamy, Prolactin related and metabolic adverse effects of atypical antipsychotic agents, J. Clin. Psychiatry 69 (Suppl. 1) (2008) 32–44.
[73] I. Tarricone, M. Casoria, B.F. Gozzi, D. Grieco, M. Menchetti, A. Serretti, et al., Metabolic risk factor profile associated with use of second generation antipsychotics: a cross sectional study in a Community Mental Health Centre, BMC Psychiatry 6 (2006) 11.
[74] J.S. Ballon, U. Pajvani, Z. Freyberg, R.L. Leibel, J.A. Lieberman, Molecular pathophysiology of metabolic effects of antipsychotic medications, Trends Endocrinol. Metab. 25 (2014) 593–600.
[75] J.M. Amiel, C.V. Mangurian, R. Ganguli, J.W. Newcomer, Addressing cardiometabolic risk during treatment with antipsychotic medications, Curr. Opin. Psychiatry 21 (2008) 613–618.
[76] J.W. Newcomer, D.W. Haupt, R. Fucetola, A.K. Melson, J.A. Schweiger, B.P. Cooper, et al., Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia, Arch. Gen. Psychiatry 59 (2002) 337–345.
[77] D.W. Haupt, J.W. Newcomer, Hyperglycemia and antipsychotic medications, J. Clin. Psychiatry 62 (Suppl. 27) (2001) 15–26.
[78] L.L. Lipscombe, L. Levesque, A. Gruneir, H.D. Fischer, D.N. Juurlink, S.S. Gill, et al., Antipsychotic drugs and hyperglycemia in older patients with diabetes, Arch. Intern. Med. 169 (2009) 1282–1289.
[79] C.M. Feek, J.S. Bevan, S. Taylor, N.S. Brown, J.D. Baird, The effect of bromocriptine on insulin secretion and glucose tolerance in patients with acromegaly, Clin. Endocrinol. (Oxf.) 15 (1981) 473–478.
[80] N. Ben Jonathan, E.R. Hugo, T.D. Brandebourg, C.R. LaPensee, Focus on prolactin as a metabolic hormone, Trends Endocrinol. Metab. 17 (2006) 110–116.
[81] B. Le Foll, A. Gallo, Y. Le Strat, L. Lu, P. Gorwood, Genetics of dopamine receptors and drug addiction: a comprehensive review, Behav. Pharmacol. 20 (2009) 1–17.
[82] B. Guigas, J.E. de Leeuw van Weenen, N. van Leeuwen, A.M. Simonis-Bik, T.W. van Haeften, G. Nijpels, et al., Sex-specific effects of naturally occurring variants in the dopamine receptor D2 locus on insulin secretion and type 2 diabetes susceptibility, Diabet. Med. 31 (2014) 1001–1008.
[83] R.I. Holt, A.J. Mitchell, Diabetes mellitus and severe mental illness: mechanisms and clinical implications, Nat. Rev. Endocrinol. 11 (2015) 79–89.
[84] S.C. Gough, M.C. O'Donovan, Clustering of metabolic comorbidity in schizophrenia: a genetic contribution? J. Psychopharmacol. 19 (2005) 47–55.
[85] Schizophrenia Working Group of the Psychiatric Genomics Consortium, Biological insights from 108 schizophrenia-associated genetic loci, Nature 511 (2014) 421–427.
[86] P.I. Lin, A.R. Shuldiner, Rethinking the genetic basis for comorbidity of schizophrenia and type 2 diabetes, Schizophr. Res. 123 (2010) 234–243.
[87] C.P. Jenkinson, R. Hanson, K. Cray, C. Wiedrich, W.C. Knowler, C. Bogardus, et al., Association of dopamine D2 receptor polymorphisms Ser311Cys and TaqIA with obesity or type 2 diabetes mellitus in Pima Indians, Int. J. Obes. Relat. Metab. Disord. 24 (2000) 1233–1238.
[88] M. Chiba, S. Suzuki, Y. Hinokio, M. Hirai, Y. Satoh, A. Tashiro, et al., Tyrosine hydroxylase gene microsatellite polymorphism associated with insulin resistance in depressive disorder, Metabolism 49 (2000) 1145–1149.
[89] A.H. Cincotta, A.H. Meier, Therapeutic process for the treatment of the pathologies of type II diabetes, [US5866584] (1999). Ref type: Patent.
[90] A.H. Cincotta, J.M. Cincotta, C.L. Pelloni, C.E. Runice, S.L. Tigner, Accelerated release composition containing bromocriptine, [US5679685] EP1258245A3 2003 (1997). Ref Type: Patent.
[91] L. Moro, A. Fiori, A. Natali, Processes for the preparation of pharmaceutical compositions containing bromocriptine having high stability and related products, EP0391374 1994 (1991). Ref type: Patent.
[92] A.J. Garber, L. Blonde, Z.T. Bloomgarden, Y. Handelsman, S. Dagogo-Jack, The role of bromocriptine-QR in the management of type 2 diabetes expert panel recommendations, Endocr. Pract. 19 (2013) 100–106.
[93] A.H. Cincotta, A.H. Meier, Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects, Diabetes Care 19 (1996) 667–670.
[94] B. Chamarthi, J.M. Gaziano, L. Blonde, A. Vinik, R.E. Scranton, M. Ezrokhi, et al., Timed bromocriptine-QR therapy reduces progression of cardiovascular disease and dysglycemia in subjects with well-controlled type 2 diabetes mellitus, J. Diabetes Res. 2015 (2015) 157698.
[95] P.W. Scislowski, E. Tozzo, Y. Zhang, S. Phaneuf, R. Prevelige, A.H. Cincotta, Biochemical mechanisms responsible for the attenuation of diabetic and obese conditions in ob/ob mice treated with dopaminergic agonists, Int. J. Obes. Relat. Metab. Disord. 23 (1999) 425–431.
[96] W. Liang, L. Gao, N. Li, B. Wang, L. Wang, Y. Wang, et al., Efficacy and safety of bromocriptine-QR in type 2 diabetes: a systematic review and meta-analysis, Horm. Metab. Res. 47 (2015) 805–812.
[97] P.R. Atkison, J.L. Mahon, J. Dupre, C.R. Stiller, M.R. Jenner, T.L. Paul, et al., Interaction of bromocriptine and cyclosporine in insulin dependent diabetes mellitus: results from the Canadian open study, J. Autoimmun. 3 (1990) 793–799.