Dopamine in Glucose Homeostasis and Type 2 Diabetes

Subjects: Medicine, General & Internal

Contributor: Giuseppe Lisco, Anna De Tullio, Michele Iovino, Olga Disoteo, Edoardo Guastamacchia, Vito Angelo Giagulli, Vincenzo Triggiani

Dopamine regulates several functions, such as voluntary movements, spatial memory, motivation, sleep, arousal, feeding, immune function, maternal behaviors, and lactation. Less clear is the role of dopamine in the pathophysiology of type 2 diabetes mellitus (T2D) and chronic complications and conditions frequently associated with it.

Keywords: dopamine ; type 2 diabetes mellitus ; insulin ; glucagon-like receptor 1 ; incretin system

1. The Effects of Dopamine on Pancreatic Islets and Insulin and Glucagon Secretion

The potential role of endogenous catecholamines in the pathogenesis of T2D was suggested by landmark studies in the 1970s [1][2][3]. The intravenous administration of L-DOPA increased the pancreatic dopamine concentration, especially within the β-cells, in normal rats [4] and inhibited insulin secretion in several species of golden hamsters [5]. A mechanistic study found that intravenous administration of L-DOPA was accompanied by a subsequent increase in the dopamine-containing grains in β-cells. Accumulation of dopamine-containing grains was found to reduce the release of insulin-containing grains by secretagogues, ultimately indicating that dopamine partially suppressed insulin release from β-cells [6]. Another study confirmed that dopamine suppresses insulin release from β-cells. The dopamine effect was completely inverted after the administration of propranolol (a β-blocker) but was not affected by dopamine antagonists, indicating that the suppression of insulin release by dopamine was mediated by α-adrenergic rather than dopaminergic signaling [7]. In an obese murine model (ob/ob), dopaminergic therapy reduced hyperglycemia and hyperlipidemia and improved islet function by restoring glucose sensitivity in β-cells (assessed by a 1.6-fold increase in the Glucokinase immunoreactivity), stabilizing hyperplasia, enhancing insulin storage, and thus reducing circulating insulin levels [8]. A recent investigation demonstrated that pancreatic islets are a site of dopamine synthesis and that L-DOPA and dopamine reduce glucose-dependent insulin secretion by dropping the frequency of intracellular oscillations of calcium currents. This effect was mediated directly by DR_3 stimulation, as demonstrated by experiments using specific dopamine antagonists [9]. In another study, a single administration of the dopamine agonist bromocriptine reduced fasting glucose and insulin levels in patients with T2D. These effects were only mild in healthy controls. They were accompanied by a reduction in prolactin levels in all and growth hormone concentrations only in T2D patients, suggesting that the bromocriptine effect on glucose control could largely depend on an insulin-sensitizing secondary impact, mainly due to a reduction in growth hormone levels [10]. Apart from the effect on insulin secretion, the proliferation rate of β-cells decreases, and the apoptosis increases following dopamine treatment [11]. An inverse correlation between circulating levels of dopamine and c-peptide (a biomarker of insulin secretion from β-cells) was demonstrated in 201 healthy voluntaries [12], in which the insulin suppressive effect of dopamine was mediated by both DR_2 and DR_3 signaling [13][14]. In a recent study on rodents, dopamine dampened glucose-stimulated insulin secretion after a meal challenge test by counteracting the incretin effect, indicating that dopamine could affect insulin secretion in the post-prandial phase [15]. Glucose intake increases circulating dopamine levels by stimulating the intestinal secretion of dopamine, and this mechanism could work as a brake effect on the incretin actions [16]. As an additional mechanism, dopamine suppresses prolactin secretion. Prolactin stimulates insulin secretion and β-cell proliferation. It plays a role in normal pancreatic development and ameliorates peripheral insulin sensitivity, especially at the level of the adipose tissue [17].

Given the anti-secretive and antiproliferative effects, dopamine may have a role in the pathophysiology of T2D. Monoaminoxidase A and B play a crucial role in the catabolism of catecholamines, including dopamine. Both isoforms are also expressed in β-cells, and a lower level of monoaminoxidase activity is associated with dampened insulin secretion. Therefore, this evidence suggests that blunted dopamine catabolism and, consequently, high intra-islet dopamine concentration may contribute to reducing insulin secretion and raising the number of apoptotic β-cells, both events

primarily involved in the pathophysiology of T2D. Interestingly, the transcription of monoaminoxidase A and B genes is under the MAF transcription factor A control [18]. MAF transcription factor A is an essential regulator of β-cell transcriptional activity since it regulates the transcription of genes involved in specific β-cell activities, including insulin biosynthesis and secretion [19]. The activity level and expression of the MAF factor A depend on glucose levels and may be reduced significantly by glucotoxicity due to hyperglycemia and chronic low-grade inflammation observed in prediabetes and diabetes [20]. Experimental models of insulinopenic, such as streptozotocin-induced, diabetes indicated that insulin deficiency increases the activity of circulating dopamine β-hydroxylase (which converts dopamine into noradrenaline), and the administration of insulin significantly reduces the enzymatic activity [21][22]. The phenomenon was associated with an increased dopamine receptor binding (up-regulation) in the striatum [23], which was the probable consequence of reduced dopamine metabolism in the same cerebral area [24][25].

These data suggest that dopamine and insulin may be involved in a potential feedback mechanism in which one negatively regulates the metabolism of the other [26].

Pivotal studies suggested that intravenous dopamine infusion stimulated glucagon release [27] in a dose-dependent manner [28]. Keck et al. found that low-dose dopamine (e.g., 2 mcg/kg/min infused for 6 consecutive hours) did not affect both insulin and glucagon secretion [29], but high-dose dopamine was found to provide relevant hyperglycemia by suppressing insulin and stimulating glucagon secretion in rats and men [27][28]. The effect could be considered an additive mechanism by which dopamine and dopamine agonists could sustain hyperglycemia in healthy and T2D patients. A summary of the mechanisms by which dopamine affects β-cell activity, insulin, and glucagon secretion is shown in **Table 1**.

Table 1. Summary of mechanisms of dopamine-mediated modulation of β-cell activity, insulin, and glucagon secretion [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28].

Mechanism	Effect	Consequences
Interference with insulin-containing grain trafficking (Dopamine-containing vesicles)	**Blunt insulin release**	• Improvement in insulin sensitivity (e.g., insulin-resistant, obese patients) • Deterioration of glucose control (non-insulin-resistant patients)
Impaired intra-pancreatic dopamine catabolism (Monoaminoxidases)	**Catecholamine-induced (alpha and D_2/D_3 receptors) suppression of insulin synthesis and secretion**	• Hyperglycemia
Meal-induced intestinal synthesis of dopamine	**Anti-incretin effect**	• Blunt insulin response after meal and post-prandial hyperglycemia
Enhancement of alpha-cell activity (High-dose dopamine)	**Glucagon secretion**	• Fasting hyperglycemia (hepatic gluconeogenesis and glycogenolysis)
Suppression of prolactin release	**Suppression of prolactin-induced insulin release**	• Hyperglycemia
Reduction in growth hormone	**Amelioration of insulin release and peripheral insulin resistance**	• Improvement in glucose control (e.g., acromegaly)

Table 1 summarizes the mechanisms by which dopamine affects β-cell activity, insulin, and glucagon secretion. Each mechanism is associated with specific effects and potentially relevant clinical consequences in terms of the progression of diabetes and deterioration of glucose control.

2. Dopamine in the Pathogenesis and Treatment of Traditional Chronic Diabetes-Related Complications

T2D and chronic comorbidities, such as arterial hypertension, overweight/obesity, and dyslipidemia, foster the development of chronic complications over time [30]. Hyperglycemia is the determinant of chronic diabetes-related complications, especially at the microvascular site, and more stringent glucose control is associated with a lower likelihood of the onset and progression of these complications [31]. Moreover, early intensive intervention to achieve optimal control of all risk factors concomitant with T2D is associated with a reduced risk of macrovascular complications [32], and the higher the stability of glucose control over time, the better the attenuation of burdens [33][34]. So far, guidelines recommend comprehensive management of T2D patients to reduce the risk of diabetes-related complications over time by targeting glucose, arterial pressure, body weight, and lipid control, as well as preventing thrombotic events and attenuating thrombotic risks [35]. Evidence is already consolidated to suggest the use of specific classes of medications, such as glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose (co)transporter 2 inhibitors (SGLT2is), to improve hard clinical outcomes, reduce the risk of adverse cardiovascular and renal endpoints, hospital admission due to heart failure and heart failure progression, and diabetes-related mortality [36][37].

The role of dopamine in the pathophysiology of diabetes-related chronic complications is an emerging issue [38]. Comprehending the mechanisms involved in the physiological activities of dopamine and the pathophysiological disruption of dopamine metabolism and dopaminergic pathways in target tissues would have relevant therapeutic implications and advance current treatments (**Table 2**). Dopaminergic neurons are described in the retina, where dopamine is a neurotransmitter. Here, dopamine diffuses through retinal layers to reach target cells and modulate their activity. Hence, the mechanism of dopamine communication in the retinal tissue is volume-dependent. In other words, dopamine deficiency or impaired metabolism/activity could be associated with retinal disease [39]. Experimental studies suggest that dopamine regulates photoreceptor activity, critical to visual adaptation to daylight [40]. Intraretinal dopamine levels are low in the early phase of retinal damage in diabetes [41], while high intraretinal levels of dopamine are protective against retinal damage and visual field loss [42]. The precise mechanism by which preserving dopamine levels in retinal tissue would prevent retinal damage and visual impairment is unclear. Experimental models found that intravitreal administration of L-DOPA was associated with lower severity of hyperglycemic memory-induced retinal microvascular alterations, including pericyte degeneration, acellular capillary and pericyte ghost generation, and endothelial apoptosis [43]. One mechanistic study in rodents has recently shown that intravitreal administration of L-DOPA reduced intraretinal levels of the vascular endothelial growth factor and insulin-like growth factor 1 receptors via the AKT/ERK pathway after 12 weeks [44]. Nevertheless, the first data available on a few cases did not confirm relevant differences in intraretinal dopamine (metabolites) in patients with diabetes without clinical signs of diabetic retinopathy and those without diabetes [45]. Additional studies are needed to verify whether intraretinal dopamine metabolism in humans differs from what has been seen in experimental models. On the other hand, the results of a pilot trial confirmed that reinforcing the intraretinal dopamine pathway may improve retinal dysfunction in the early stages of diabetic retinopathy [46]. So far, concrete pathophysiological hypotheses suggest a link between neurodegenerative disease and diabetic retinopathy in T2D [47], and evidence supports the role of diagnostic intervention in the early stages of both diseases [48]. From a therapeutic viewpoint, specific trials are currently ongoing to investigate the role of dopamine replacement in early-stage diabetic retinopathy and diabetic macular edema (NCT05132660; NCT02706977; NCT03161652). GLP-1 agonists may accelerate the progression of diabetic retinopathy and can be associated with adverse retinal outcomes while improving glucose control. Although evidence is discordant, data from the literature reported that this effect could be restricted to only some specific analogs and could be related to some background characteristics, such as poor glycemic control, more rapid achievement of glucose targets, higher body weight, and the presence of very high cardiovascular risk [49][50]. The above results align with preclinical evidence suggesting that GLP-1 analogs promote endothelial cell growth and angiogenesis. It could be interesting to assess the role of GLP-1 analogs on the intraretinal dopaminergic pathway. One trial could clarify this issue (NCT02671864).

Dopamine and DRs in the nephron tubules are essential in regulating key renal functions, such as electrolytes and water resorption, acid–base balance, and blood pressure regulation. DR_1 and DR_2 are the most widely expressed receptors mediating dopamine activity in the whole body [51]. In chronic diseases, such as arterial hypertension and diabetes, the expression of dopamine receptors could be significantly impaired in the kidney and the dopamine metabolism altered [52]. Because of these detrimental mechanisms, water exertion and natriuresis can be substantially reduced, thus contributing to water and sodium retention, increased blood pressure, glomerular hyperfiltration, and micro-/macroalbuminuria [53]. Experimental data in rats suggested that high intrarenal levels of dopamine prevent the mentioned effects and protect against glomerular injury and progression of diabetic nephropathy [54]. One pilot study found that administering bromocriptine (a dopamine agonist) compared to placebo reduced blood pressure and the left ventricular mass index without deteriorating the glomerular filtration rate in T2D over 6 months of treatment [55].

Dopamine plays many actions in the human heart, including positive inotropic and chronotropic effects, regulation of coronary flow, and cardiomyocyte metabolism [56]. These effects are mediated directly by dopamine and its interaction with DRs or indirectly by dopamine and noradrenaline action on α-adrenergic receptors [57]. Early evidence suggested the existence of impaired intracardiac dopamine metabolism in patients with diabetes [58]. More recent evidence suggests that early morning dopamine deficiency, frequently described in obese and T2D individuals, is involved in the overactivation of the sympathetic tone and release of corticotropin-stimulating hormone by the hypothalamic paraventricular nucleus. These effects produce substantial variability in daily heart rate, an indicator of cardiac autonomic neuropathy, and are associated with adverse events and dysmetabolic consequences on glucose control [59]. DR_2 agonists may improve hemodynamics in T2D patients with heart failure (HF), positively affecting heart-failure-related outcomes [60]. Nevertheless, ergot-derived dopamine agonists are known for their cardiotoxicity due to their co-agonism with serotoninergic receptors [61]. Especially when administered at high doses, ergot-derived dopamine agonists are associated with myocardial valvopathy, thrombosis, arrhythmic events, and HF [61][62]. Antagonizing the serotoninergic effects of these agents may be considered a possible therapeutic strategy in diabetes-related HF [63]. From a therapeutic viewpoint, dopamine agents provide controversial evidence in terms of improvement in hemodynamics, preservation of renal function, and potassium homeostasis while on loop diuretics in advanced and acutely decompensated HF. Combining low-dose dopamine with low-dose loop diuretics effectively improves hemodynamic parameters and preserves glomerular filtration rate deterioration compared to high-dose loop diuretics alone [64]. Nevertheless, the results of two randomized clinical trials did not confirm the efficacy of low-dose dopamine in combination with both low-dose and high-dose diuretics in this clinical setting [65][66]. It is unclear if dopaminergic agents may be therapeutic in less severe clinical stages of HF to prevent adverse outcomes and reduce the risk of hospital admission due to symptomatic HF, but more investigation is ongoing (NCT01901809). It is unclear if positive results provided by SGLT2is on HF-related outcomes could depend, at least in part, on improved intracardiac dopamine metabolism.

Neurologic effects after ischemic stroke largely depend on the location and extension of ischemic areas, time of exposure to ischemic reperfusion injury, and baseline cerebral performance. Generally, ischemic stroke impairs dopamine release, synthesis, and DR activity in the striatum [67]. Dopamine deficiency is associated with cognitive and motor impairment, and evidence suggests that treatments restoring dopamine levels may improve recovery after stroke [68][69]. The mechanisms explaining this potential are that dopamine enhances motivation and improves symptoms of neuropsychiatric disorders related to stroke, complicating the rehabilitative period [70][71]. Nevertheless, no evidence has been provided to confirm the therapeutic rationale as a pharmacological strategy to improve relevant endpoints during post-stroke rehabilitation [72][73]. It is unknown if certain medications, such as thiazolidinediones, GLP-1RAs, and SGLT2is, may affect intracerebral dopamine metabolism as one of the mechanisms by which they benefit the prevention of ischemic stroke.

Table 2. Summary of evidence highlighting the role of dopamine in the pathogenesis of diabetes-related chronic complications and implication for therapy.

Diabetes-Related Traditional Chronic Complication	Role of Dopamine	Effect	Rationale for Treatment (Dopamine Agonists or Levodopa)
Retinopathy [40][41][42][43][44][45][46][47][48][49][50]	**Impaired intraretinal metabolism (deficiency)**	**Defective photoreceptor adaptation to light**	**Yes**
Chronic renal disease [51][52][53][54][55]	**Impaired renal metabolism (glomerular filtration-depended reduction)**	**Dysregulation in water and natrium resorption; promotion of glomerular hyperfiltration; micro- and macroalbuminuria**	**Scanty evidence or negative results**
Neuropathy [59][60][61]	**Defective axonal transport; impaired metabolism (accumulation due to inadequate conversion to noradrenaline?)**	**Implication for painful neuropathy**	**No (dopamine antagonists)**
Stroke [67][68][69][70][71][72][73]	**Impaired cerebral metabolism (deficiency)**	**Loss of motivation, motor impairment, and pathogenic role in post-stroke neuropsychiatric disorder**	**Scanty evidence or negative results**
Cardiovascular diseases [56][57][58][59][60][61][62][63][64][65]	**Impaired cardiac metabolism (accumulation due to inadequate conversion to noradrenaline?); striatal deficiency**	**Increased risk of heart failure, impaired coronary vasodilatation, cardiac autonomic neuropathy**	**Scanty evidence or negative results**

Table 2 summarizes the leading evidence indicating the role of dopamine in the pathophysiology of traditional diabetes-related chronic complications.

References

1. Quickel, K.E., Jr.; Feldman, J.M.; Lebovitz, H.E. Enhancement of insulin secretion in adult onset diabetics by methysergide maleate: Evidence for an endogenous biogenic monoamine mechanism as a factor in the impaired insulin secretion in diabetes mellitus. J. Clin. Endocrinol. Metab. 1971, 33, 877–881.
2. Lundquist, I. Insulin secretion. Its regulation by monoamines and acid amyloglucosidase. Acta Physiol. Scand. Suppl. 1971, 372, 1–47.
3. Lebovitz, H.E.; Feldman, J.M. Pancreatic biogenic amines and insulin secretion in health and disease. Fed. Proc. 1973, 32, 1797–1802.
4. Gagliardino, J.J.; Iturriza, F.C.; Hernandez, R.E.; Zieher, L.M. Effect of catecholamines precursors on insulin secretion. Endocrinology 1970, 87, 823–825.
5. Quickel, K.E., Jr.; Feldman, J.M.; Lebovitz, H.E. Inhibition of insulin secretion by serotonin and dopamine: Species variation. Endocrinology 1971, 89, 1295–1302.
6. Ericson, L.E.; Håkanson, R.; Lundquist, I. Accumulation of dopamine in mouse pancreatic B-cells following injection of L-DOPA. Localization to secretory granules and inhibition of insulin secretion. Diabetologia 1977, 13, 117–124.
7. Itoh, M.; Furman, B.L.; Gerich, J.E. Dopaminergic suppression of pancreatic somatostatin secretion. Acta Endocrinol. 1982, 101, 56–61.
8. Jetton, T.L.; Liang, Y.; Cincotta, A.H. Systemic treatment with sympatholytic dopamine agonists improves aberrant β-cell hyperplasia and GLUT2, glucokinase, and insulin immunoreactive levels in ob/ob mice. Metabolism 2001, 50, 1377–1384.
9. Ustione, A.; Piston, D.W. Dopamine synthesis and D3 receptor activation in pancreatic β-cells regulates insulin secretion and intracellular oscillations. Mol. Endocrinol. 2012, 26, 1928–1940.
10. Barnett, A.H.; Chapman, C.; Gailer, K.; Hayter, C.J. Effect of bromocriptine on maturity onset diabetes. Postgrad. Med. J. 1980, 56, 11–14.
11. Garcia Barrado, M.J.; Iglesias Osma, M.C.; Blanco, E.J.; Carretero Hernández, M.; Sánchez Robledo, V.; Catalano Iniesta, L.; Carrero, S.; Carretero, J. Dopamine modulates insulin release and is involved in the survival of rat pancreatic beta cells. PLoS ONE 2015, 10, e0123197.
12. Tomaschitz, A.; Ritz, E.; Kienreich, K.; Pieske, B.; März, W.; Boehm, B.O.; Drechsler, C.; Meinitzer, A.; Pilz, S. Circulating dopamine and C-peptide levels in fasting nondiabetic hypertensive patients: The Graz Endocrine Causes of Hypertension study. Diabetes Care 2012, 35, 1771–1773.
13. Simpson, N.; Maffei, A.; Freeby, M.; Burroughs, S.; Freyberg, Z.; Javitch, J.; Leibel, R.L.; Harris, P.E. Dopamine-mediated autocrine inhibitory circuit regulating human insulin secretion in vitro. Mol. Endocrinol. 2012, 26, 1757–1772.
14. Kopf, D.; Gilles, M.; Paslakis, G.; Medlin, F.; Lederbogen, F.; Lehnert, H.; Deuschle, M. Insulin secretion and sensitivity after single-dose amisulpride, olanzapine or placebo in young male subjects: Double blind, cross-over glucose clamp study. Pharmacopsychiatry 2012, 45, 223–228.
15. Maffei, A.; Segal, A.M.; Alvarez-Perez, J.C.; Garcia-Ocaña, A.; Harris, P.E. Anti-incretin, Anti-proliferative Action of Dopamine on β-Cells. Mol. Endocrinol. 2015, 29, 542–557.
16. Tavares, G.; Rosendo-Silva, D.; Simões, F.; Eickhoff, H.; Marques, D.; Sacramento, J.F.; Capucho, A.M.; Seiça, R.; Conde, S.V.; Matafome, P. Circulating Dopamine Is Regulated by Dietary Glucose and Controls Glucagon-like 1 Peptide Action in White Adipose Tissue. Int. J. Mol. Sci. 2023, 24, 2464.
17. Chien, H.Y.; Chen, S.M.; Li, W.C. Dopamine receptor agonists mechanism of actions on glucose lowering and their connections with prolactin actions. Front. Clin. Diabetes Healthc. 2023, 4, 935872.
18. Ganic, E.; Johansson, J.K.; Bennet, H.; Fex, M.; Artner, I. Islet-specific monoamine oxidase A and B expression depends on MafA transcriptional activity and is compromised in type 2 diabetes. Biochem. Biophys. Res. Commun. 2015, 468, 629–635.
19. Available online: https://www.ncbi.nlm.nih.gov/gene/389692 (accessed on 31 August 2023).
20. Oetjen, E.; Blume, R.; Cierny, I.; Schlag, C.; Kutschenko, A.; Krätzner, R.; Stein, R.; Knepel, W. Inhibition of MafA transcriptional activity and human insulin gene transcription by interleukin-1beta and mitogen-activated protein kinase

kinase kinase in pancreatic islet beta cells. Diabetologia 2007, 50, 1678–1687.

21. Schmidt, R.E.; Geller, D.M.; Johnson, E.M., Jr. Characterization of increased plasma dopamine-β-hydroxylase activity in rats with experimental diabetes. Diabetes 1981, 30, 416–423.
22. Hurst, J.H.; Nisula, B.C.; Stolk, J.M. Circulating dopamine-β-hydroxylase in the rat: Importance of altered disposal pathways in experimental diabetes. J. Pharmacol. Exp. Ther. 1982, 220, 108–114.
23. Lozovsky, D.; Saller, C.F.; Kopin, I.J. Dopamine receptor binding is increased in diabetic rats. Science 1981, 214, 1031–1033.
24. Kwok, R.P.; Juorio, A.V. Concentration of striatal tyramine and dopamine metabolism in diabetic rats and effect of insulin administration. Neuroendocrinology 1986, 43, 590–596.
25. Kwok, R.P.; Walls, E.K.; Juorio, A.V. The concentration of dopamine, 5-hydroxytryptamine, and some of their acid metabolites in the brain of genetically diabetic rats. Neurochem. Res. 1985, 10, 611–616.
26. Chaudhry, S.; Bernardes, M.; Harris, P.E.; Maffei, A. Gastrointestinal dopamine as an anti-incretin and its possible role in bypass surgery as therapy for type 2 diabetes with associated obesity. Minerva Endocrinol. 2016, 41, 43–56.
27. Leblanc, H.; Lachelin, G.C.; Abu-Fadil, S.; Yen, S.S. The effect of dopamine infusion on insulin and glucagon secretion in man. J. Clin. Endocrinol. Metab. 1977, 44, 196–198.
28. Pernet, A.; Hammond, V.A.; Blesa-Malpica, G.; Burrin, J.; Orskov, H.; Alberti, K.G.; Johnston, D.G. The metabolic effects of dopamine in man. Eur. J. Clin. Pharmacol. 1984, 26, 23–28.
29. Keck, F.S.; Foldenauer, A.; Wolf, C.F.; Zeller, G.; Meyerhoff, C.; Dolderer, M.; Loos, U.; Pfeiffer, E.F. Differential effects of dopamine on glucoregulatory hormones in rats. Diabetes Res. Clin. Pract. 1990, 8, 155–159.
30. Deshpande, A.D.; Harris-Hayes, M.; Schootman, M. Epidemiology of diabetes and diabetes-related complications. Phys. Ther. 2008, 88, 1254–1264.
31. Gaster, B.; Hirsch, I.B. The effects of improved glycemic control on complications in type 2 diabetes. Arch. Intern. Med. 1998, 158, 134–140.
32. Nørgaard, C.H.; Mosslemi, M.; Lee, C.J.; Torp-Pedersen, C.; Wong, N.D. The Importance and Role of Multiple Risk Factor Control in Type 2 Diabetes. Curr. Cardiol. Rep. 2019, 21, 35.
33. Monnier, L.; Colette, C.; Schlienger, J.L.; Bauduceau, B.; ROwens, D. Glucocentric risk factors for macrovascular complications in diabetes: Glucose ‘legacy’ and ‘variability’-what we see, know and try to comprehend. Diabetes Metab. 2019, 45, 401–408.
34. Ceriello, A.; Prattichizzo, F. Variability of risk factors and diabetes complications. Cardiovasc. Diabetol. 2021, 20, 101.
35. ElSayed, N.A.; Aleppo, G.; Aroda, V.R.; Bannuru, R.R.; Brown, F.M.; Bruemmer, D.; Collins, B.S.; Hilliard, M.E.; Isaacs, D.; Johnson, E.L.; et al. Addendum. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Care in Diabetes–2023. Diabetes Care 2023, 46 (Suppl. S1), S41–S48, Erratum in Diabetes Care 2023, 46, 1716–1717.
36. Davies, M.J.; Drexel, H.; Jornayvaz, F.R.; Pataky, Z.; Seferović, P.M.; Wanner, C. Cardiovascular outcomes trials: A paradigm shift in the current management of type 2 diabetes. Cardiovasc. Diabetol. 2022, 21, 144.
37. Dardano, A.; Miccoli, R.; Bianchi, C.; Daniele, G.; Del Prato, S. Invited review. Series: Implications of the recent CVOTs in type 2 diabetes: Which patients for GLP-1RA or SGLT-2 inhibitor? Diabetes Res. Clin. Pract. 2020, 162, 108112.
38. Gasecka, A.; Siwik, D.; Gajewska, M.; Jaguszewski, M.J.; Mazurek, T.; Filipiak, K.J.; Postuła, M.; Eyileten, C. Early Biomarkers of Neurodegenerative and Neurovascular Disorders in Diabetes. J. Clin. Med. 2020, 9, 2807.
39. Popova, E. Role of Dopamine in Retinal Function. In Webvision: The Organization of the Retina and Visual System; Kolb, H., Fernandez, E., Nelson, R., Eds.; University of Utah Health Sciences Center: Salt Lake City, UT, USA, 1995. Available online: https://www.ncbi.nlm.nih.gov/books/NBK561740/ (accessed on 28 May 2020).
40. Jain, V.; Liang, P.J.M.; Raja, S.; Mikhael, M.; Cameron, M.A. Light activation of the dopaminergic system occurs after eye-opening in the mouse retina. Front. Ophthalmol. 2023, 3, 1184627.
41. Wubben, T.J. Dopamine and Early Retinal Dysfunction in Diabetes: Insights From a Phase 1 Study. Diabetes 2020, 69, 1339–1340.
42. Allen, R.S.; Khayat, C.T.; Feola, A.J.; Win, A.S.; Grubman, A.R.; Chesler, K.C.; He, L.; Dixon, J.A.; Kern, T.S.; Iuvone, P.M.; et al. Diabetic rats with high levels of endogenous dopamine do not show retinal vascular pathology. Front. Neurosci. 2023, 17, 1125784.
43. Lee, Y.J.; Jeon, H.Y.; Lee, A.J.; Kim, M.; Ha, K.S. Dopamine ameliorates hyperglycemic memory-induced microvascular dysfunction in diabetic retinopathy. FASEB J. 2022, 36, e22643.

44. Upreti, S.; Sen, S.; Nag, T.C.; Ghosh, M.P. Insulin like growth factor-1 works synergistically with dopamine to attenuate diabetic retinopathy by downregulating vascular endothelial growth factor. Biomed. Pharmacother. 2022, 149, 112868.

45. Hendrick, A.; Smith, J.; Stelton, C.; Barb, S.; Yan, J.; Cribbs, B.; Jain, N.; Yeh, S.; Hubbard, G.B.; He, L.; et al. Dopamine metabolite levels in the vitreous of diabetic and non-diabetic humans. Exp. Eye Res. 2020, 195, 108040.

46. Motz, C.T.; Chesler, K.C.; Allen, R.S.; Bales, K.L.; Mees, L.M.; Feola, A.J.; Maa, A.Y.; Olson, D.E.; Thule, P.M.; Iuvone, P.M.; et al. Novel Detection and Restorative Levodopa Treatment for Preclinical Diabetic Retinopathy. Diabetes 2020, 69, 1518–1527.

47. Zhang, Z.; Zhou, Y.; Zhao, H.; Xu, J.; Yang, X. Association Between Pathophysiological Mechanisms of Diabetic Retinopathy and Parkinson's Disease. Cell. Mol. Neurobiol. 2022, 42, 665–675.

48. Chen, P.; Li, J.; Li, Z.; Yu, D.; Ma, N.; Xia, Z.; Meng, X.; Liu, X. 18F-FP-CIT dopamine transporter PET findings in the striatum and retina of type 1 diabetic rats. Ann. Nucl. Med. 2023, 37, 219–226.

49. Bethel, M.A.; Diaz, R.; Castellana, N.; Bhattacharya, I.; Gerstein, H.C.; Lakshmanan, M.C. HbA1c Change and Diabetic Retinopathy During GLP-1 Receptor Agonist Cardiovascular Outcome Trials: A Meta-analysis and Meta-regression. Diabetes Care 2021, 44, 290–296.

50. Kapoor, I.; Sarvepalli, S.M.; D'Alessio, D.; Grewal, D.S.; Hadziahmetovic, M. GLP-1 receptor agonists and diabetic retinopathy: A meta-analysis of randomized clinical trials. Surv. Ophthalmol. 2023, 68, 1071–1083.

51. Olivares-Hernández, A.; Figuero-Pérez, L.; Cruz-Hernandez, J.J.; González Sarmiento, R.; Usategui-Martin, R.; Miramontes-González, J.P. Dopamine Receptors and the Kidney: An Overview of Health- and Pharmacological-Targeted Implications. Biomolecules 2021, 11, 254.

52. Matsuyama, T.; Ohashi, N.; Ishigaki, S.; Isobe, S.; Tsuji, N.; Fujikura, T.; Tsuji, T.; Kato, A.; Miyajima, H.; Yasuda, H. The Relationship between the Intrarenal Dopamine System and Intrarenal Renin-angiotensin System Depending on the Renal Function. Intern. Med. 2018, 57, 3241–3247.

53. Hirose, M.; Tomoda, F.; Koike, T.; Yamazaki, H.; Ohara, M.; Liu, H.; Kagitani, S.; Inoue, H. Imbalance of renal production between 5-hydroxytryptamine and dopamine in patients with essential hypertension complicated by microalbuminuria. Am. J. Hypertens. 2013, 26, 227–233.

54. Zhang, M.Z.; Yao, B.; Yang, S.; Yang, H.; Wang, S.; Fan, X.; Yin, H.; Fogo, A.B.; Moeckel, G.W.; Harris, R.C. Intrarenal dopamine inhibits progression of diabetic nephropathy. Diabetes 2012, 61, 2575–2584.

55. Mejía-Rodríguez, O.; Herrera-Abarca, J.E.; Ceballos-Reyes, G.; Avila-Diaz, M.; Prado-Uribe, C.; Belio-Caro, F.; Salinas-González, A.; Vega-Gomez, H.; Alvarez-Aguilar, C.; Lindholm, B.; et al. Cardiovascular and renal effects of bromocriptine in diabetic patients with stage 4 chronic kidney disease. Biomed. Res. Int. 2013, 2013, 104059.

56. Neumann, J.; Hofmann, B.; Dhein, S.; Gergs, U. Role of Dopamine in the Heart in Health and Disease. Int. J. Mol. Sci. 2023, 24, 5042.

57. Lokhandwala, M.F.; Barrett, R.J. Cardiovascular dopamine receptors: Physiological, pharmacological and therapeutic implications. J. Auton. Pharmacol. 1982, 2, 189–215.

58. Neubauer, B.; Christensen, N.J. Norepinephrine, epinephrine, and dopamine contents of the cardiovascular system in long-term diabetics. Diabetes 1976, 25, 6–10.

59. Vinik, A.I.; Casellini, C.; Parson, H.K.; Colberg, S.R.; Nevoret, M.L. Cardiac Autonomic Neuropathy in Diabetes: A Predictor of Cardiometabolic Events. Front. Neurosci. 2018, 12, 591.

60. Vijayakumar, S.; Vaduganathan, M.; Butler, J. Glucose-Lowering Therapies and Heart Failure in Type 2 Diabetes Mellitus: Mechanistic Links, Clinical Data, and Future Directions. Circulation 2018, 137, 1060–1073.

61. Frishman, W.H.; Grewall, P. Serotonin and the heart. Ann. Med. 2000, 32, 195–209.

62. Mokhles, M.M.; Trifirò, G.; Dieleman, J.P.; Haag, M.D.; van Soest, E.M.; Verhamme, K.M.; Mazzaglia, G.; Herings, R.; de Luise, C.; Ross, D.; et al. The risk of new onset heart failure associated with dopamine agonist use in Parkinson's disease. Pharmacol. Res. 2012, 65, 358–364.

63. Fouad Shalaby, M.A.; Abd El Latif, H.A.; El Yamani, M.; Galal, M.A.; Kamal, S.; Sindi, I.; Masaood, R. Therapeutic activity of sarpogrelate and dopamine D2 receptor agonists on cardiovascular and renal systems in rats with alloxan-induced diabetes. BMC Pharmacol. Toxicol. 2021, 22, 64.

64. Giamouzis, G.; Butler, J.; Starling, R.C.; Karayannis, G.; Nastas, J.; Parisis, C.; Rovithis, D.; Economou, D.; Savvatis, K.; Kirlidis, T.; et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: Results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J. Card. Fail. 2010, 16, 922–930.

65. Triposkiadis, F.K.; Butler, J.; Karayannis, G.; Starling, R.C.; Filippatos, G.; Wolski, K.; Parissis, J.; Parisis, C.; Rovithis, D.; Koutrakis, K.; et al. Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion:

The Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. Int. J. Cardiol. 2014, 172, 115–121.

66. Sharma, K.; Vaishnav, J.; Kalathiya, R.; Hu, J.R.; Miller, J.; Shah, N.; Hill, T.; Sharp, M.; Tsao, A.; Alexander, K.M.; et al. Randomized Evaluation of Heart Failure With Preserved Ejection Fraction Patients With Acute Heart Failure and Dopamine: The ROPA-DOP Trial. JACC Heart Fail. 2018, 6, 859–870.
67. Gower, A.; Tiberi, M. The Intersection of Central Dopamine System and Stroke: Potential Avenues Aiming at Enhancement of Motor Recovery. Front. Synaptic Neurosci. 2018, 10, 18.
68. Vitrac, C.; Nallet-Khosrofian, L.; Iijima, M.; Rioult-Pedotti, M.S.; Luft, A. Endogenous dopamine transmission is crucial for motor skill recovery after stroke. IBRO Neurosci. Rep. 2022, 13, 15–21.
69. Stinear, C.M. Dopamine for motor recovery after stroke: Where to from here? Lancet Neurol. 2019, 18, 514–515.
70. Sami, M.B.; Faruqui, R. The effectiveness of dopamine agonists for treatment of neuropsychiatric symptoms post brain injury and stroke. Acta Neuropsychiatr. 2015, 27, 317–326.
71. Villa, M.; Martínez-Vega, M.; Del Pozo, A.; Muneta-Arrate, I.; Gómez-Soria, A.; Muguruza, C.; de Hoz-Rivera, M.; Romero, A.; Silva, L.; Callado, L.F.; et al. The Role of the Dopamine System in Post-Stroke Mood Disorders in Newborn Rats. Int. J. Mol. Sci. 2023, 24, 3229.
72. Ford, G.A.; Bhakta, B.B.; Cozens, A.; Cundill, B.; Hartley, S.; Holloway, I.; Meads, D.; Pearn, J.; Ruddock, S.; Sackley, C.M.; et al. Dopamine Augmented Rehabilitation in Stroke (DARS): A multicentre double-blind, randomised controlled trial of co-careldopa compared with placebo, in addition to routine NHS occupational and physical therapy, delivered early after stroke on functional recovery. Effic. Mech. Eval. 2019, 6, 1–172.
73. Scheidtmann, K.; Fries, W.; Müller, F.; Koenig, E. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: A prospective, randomised, double-blind study. Lancet 2001, 358, 787–790.
