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Dopamine outside the brain: The eye, cardiovascular system and endocrine pancreas

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ABSTRACT

Dopamine (DA) and DA receptors (DR) have been extensively studied in the central nervous system (CNS), but their role in the periphery is still poorly understood. Here we summarize data on DA and DRs in the eye, cardiovascular system and endocrine pancreas, three districts where DA and DA-related drugs have been studied and the expression of DR documented. In the eye, DA modulates ciliary blood flow and aqueous production, which impacts on intraocular pressure and glaucoma. In the cardiovascular system, DA increases blood pressure and heart activity, mostly through a stimulation of adrenoceptors, and induces vasodilatation in the renal circulation, possibly through D1R stimulation. In pancreatic islets, beta cells store DA and co-release it with insulin. D1R is mainly expressed in beta cells, where it stimulates insulin release, while D2R is expressed in both beta and delta cells (in the latter at higher level), where it inhibits, respectively, insulin and somatostatin release. The formation of D2R-somatostatin receptor 5 heteromers (documented in the CNS), might add complexity to the system. DA may exert both direct autocrine effects on beta cells, and indirect paracrine effects through delta cells and somatostatin. Bromocriptine, an FDA approved drug for diabetes, endowed with both D1R (antagonistic) and D2R (agonistic) actions, may exert complex effects, resulting from the integration of direct effects on beta cells and paracrine effects from delta cells. A full comprehension of peripheral DA signaling deserves further studies that may generate innovative therapeutic drugs to manage conditions such as glaucoma, cardiovascular diseases and diabetes.

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Abbreviations: AC, Adenylyl cyclase; AH, Aqueous humor; α1AR, Alpha1-adrenoceptor; βAR, Beta-adrenoceptor; CICR, Calcium-induced calcium release; cAMP, Cyclic adenosine monophosphate; CaV, Voltage-gated Ca^{2+} channels; cGMP, Cyclic guanosine monophosphate; CNS, Central nervous system; DA, Dopamine; DAG, Diacylglycerol; DR, Dopamine receptor; D(1–5)R, Dopamine receptor (1–5); EC, Endothelial cell; EPAC, Exchange proteins activated by cAMP; EPI, Epinephrine; GIRK, G protein-coupled inwardly-rectifying potassium channels; GPCR, G protein-coupled receptors; GRK, G-protein-coupled receptor kinase; HAEC, Human aortic endothelial cells; HUVEC, Human umbilical vein endothelial cells; IHC, Immunohistochemistry; IOP, Intraocular pressure; IP_3, Inositol 1,4,5-trisphosphate; ISH, in situ hybridization; i.v., Intravenous; L-DOPA, L-3,4-Dihydroxyphenylalanine; NE, Norepinephrine; PD, Parkinson's disease; PKA, Protein kinase A; PLC, Phospholipase C; PIP_2, Phosphatidylinositol diphosphate; RT-PCR, Reverse transcription-polymerase chain reaction; sGC, Soluble guanylyl cyclase; SPET, Single-photon emission tomography; SST, Somatostatin; SSTR, Somatostatin receptor; SSTR(2–5), Somatostatin receptor (2–5); T2D, Type 2 diabetes; TH, Tyrosine hydroxylase; VMAT2, Vesicular monoamine transporter 2; VSMC, Vascular smooth muscle cell; WT, Wild-type; WB, Western blot.

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1. Introduction

Dopaminergic neurotransmission is implicated in the pathophysiology of major neuropsychiatric disorders, including Parkinson's disease (PD) and schizophrenia. The study of dopamine (DA) and dopaminergic transmission has contributed to the development of relevant drugs, such as L-DOPA, bromocriptine, haloperidol, clozapine, and many others, which act via dopaminergic mechanisms. Four main dopaminergic pathways have been identified within the central nervous system (CNS). The ventral tegmental area is the place of origin of two projection pathways towards the cortex (the mesocortical pathway) and the limbic area (the mesolimbic pathway); the hypothalamus is the place of origin of a projection towards the pituitary gland which controls prolactin secretion (the tuberoinfundibular pathway) and a dopaminergic projection extends from the substantia nigra to the striatum (the nigrostriatal pathway). DA acts on specific receptors, belonging to the G protein-coupled receptor family. Five genes encoding DA receptors (DRs) have been identified. These receptors are divided in two subfamilies: the D1-like receptor subtypes (D1R and D5R), coupled to Gs, activating adenylyl cyclase and the D2-like subfamily (D2R, D3R, and D4R) coupled to Gi, inhibiting adenylyl cyclase (Missale, Nash, Robinson, Jaber, & Caron, 1998). D1R and D2R are the most abundant subtypes in the CNS, but D1R is the most widespread (Fremeau Jr. et al., 1991). D5R is expressed at a much lower level than D1R and its distribution is limited to the hippocampus and thalamus (the lateral mammillary nucleus and the parafascicular nucleus of the thalamus) (Ciliax et al., 2000). D2R is located mainly in the striatum, olfactory tubercle, nucleus accumbens, substantia nigra pars compacta, ventral tegmental area and pituitary gland. D2R and D3R are pre- and post-synaptic, unlike D1R and D5R, which are mainly post-synaptic receptors (McGinnis, Siciliano, & Jones, 2016; Radl et al., 2018). D4R is found, at a lower expression, in the basal ganglia and at a higher expression in the frontal cortex, medulla, amygdala, hypothalamus and mesencephalon; however in these areas, D4R expression remains below the expression level of other DRs (Valerio et al., 1994). D3R is expressed in several brain areas (mesencephalon, nucleus accumbens, olfactory tubercle and islands of Calleja, striatum, PFC, and hippocampus) (Leggio, Bucolo, Platania, Salomone, & Drago, 2016).

In addition to acting as monomers, DRs constitute, within and outside the brain, dimeric and/or oligomeric complexes by association of a single species (homodimer, homomer) or different species (heterodimer, heteromer); in this latter case the association may involve not only different DR subtypes, but also other G protein-coupled receptors (GPCR) and even ligand-gated channels. Heteromerization has been documented for D1R and D2R (Lee et al., 2004), D1R and D3R (Fiorentini et al., 2008; Marcellino et al., 2008; Zeng et al., 2004), D2R and D3R (Maggio, Scarselli, Novi, Millan, & Corsini, 2003; Novi, Millan, Corsini, & Maggio, 2007; Scarselli et al., 2001). As regards other GPSRs, heteromers may occur between D1R and adenosine A1 receptors (Gines et al., 2000), D2R/D3R and adenosine A2 receptors (Hillion et al., 2002; Torvinen et al., 2005), D2R and somatostatin (SST) receptor (SSTR) 5 (SSTR5) (Rocheville et al., 2000). Dimer formation influences key aspects of receptor function, including ligand recognition and binding, signaling and membrane trafficking (Kabbani & Levenson, 2007). For instance, D2R-SSTR5 oligomers are characterized by a much greater affinity for DA and somatostatin and display enhanced G protein and effector coupling to adenylyl cyclase as compared to each respective homodimer (Fig. 1) (Kabbani & Levenson, 2007). Moreover, while the prevailing view is that DRs act through G proteins, DRs may also activate G protein-independent mechanisms. These mechanisms typically involve G-protein-coupled receptor kinases (GRKs) and arrestins. Upon repeated and/or maximal receptor stimulation, GRKs phosphorylate GPCRs and, by so doing, make them prone to the interaction with arrestins, which represents the basis of homologous desensitization (Gurevich & Gurevich, 2019). However, because arrestins are scaffold proteins regulating the interaction of various signaling proteins with

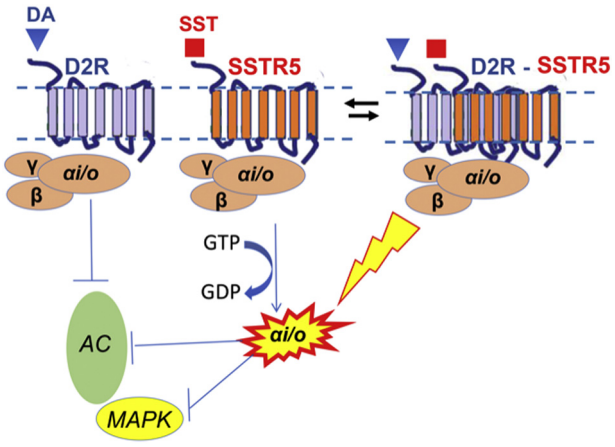

Fig. 1. Schematic illustration showing heterodimerization of dopamine D2 receptor with somatostatin receptor 5 and consequent modulation of downstream signaling. The formation of D2R-SSTR5 heterodimers enhances the inhibitory effect on adenylyl cyclase (AC) and may affect additional signaling, such as mitogen-activated protein kinases (MAPK).

receptors, not only they induce the suppression of G protein signaling (desensitization, down-regulation), but also promote G protein-independent signaling. This phenomenon has been largely studied for DRs in CNS; for example, the reduced response to drugs that enhance DA neurotransmission in β-arrestin 2 knockout mice indicates that β-arrestin 2 participates in DR signaling. In particular, β-arrestin 2 is considered to act as an intermediate in the regulation of Akt and GSK-3 following DR stimulation (Beaulieu et al., 2005).

Many studies have generated a plethora of data on DA neurotransmission in the CNS, but the role of peripheral (i.e. outside the CNS) DA is still poorly understood. DRs outside the brain have been identified in diverse organs and tissues, including vascular beds, heart, gastrointestinal tract, eye, kidney and pancreas (Beaulieu & Gainetdinov, 2011; Bucolo et al., 2012; De Mei, Ramos, Iitaka, & Borrelli, 2009; Missale et al., 1998). Circulating DA levels attain 15–30 pg/mL (0.1–0.2 nmol/L), coming mainly from spilling over from noradrenergic nerves (Goldstein & Holmes, 2008). This concentration is far below the dissociation constant of DA for DRs, but it might be substantially higher and attain a level sufficient for DR activation in the proximity of vascular receptors, particularly those located in vascular smooth muscle cells receiving sympathetic nerve endings. Several studies also report a variable expression and distribution of DRs in immune cells (Bergquist & Silberring, 1998) and DA seems to exert anticancer effects through immunomodulation (Basu, Dasgupta, & Chowdhury, 1995). In kidneys, DA is synthesized and secreted from proximal tubule cells and decreases sodium transport; alteration of DA signaling has been proposed to play a role in some hypertensive states (Gildea et al., 2010). As discussed below in more detail, DRs are expressed in eye, in cardiovascular system and in pancreatic cells, while DA is synthesized and released by endothelial cells (EC) and pancreatic beta cells. The potential paracrine and autocrine action of DA in the eye, the cardiovascular system and the endocrine pancreas represents the main aim of this review.

2. Dopamine and the eye (excluding retina)

Dopamine (DA) and dopaminergic signaling has been extensively studied in the retina. During embryonic development, the retina and optic nerve extend from diencephalon, and are thus considered part of the CNS. For these reasons this chapter is focused on DA and the peripheral ocular tissues such as cornea, aqueous humor, trabecular meshwork, uveo-sclera, and iris-ciliary body.

In both rabbit and human eyes, DA was found to be the most abundant catecholamine in the central and intermediate segments of the cornea, whilst in the peripheral segments norepinephrine (NE) was

Table 1
Dopamine receptor expression in peripheral eye.

Species	Dopamine receptor subtype	Tissue	Method	Function	Reference
Bovine, mouse	D1	Ciliary body	RT-PCR	↑ AH inflow	Lograno, Daniele, & Govoni, 1990; Piltz et al., 1998; Bucolo et al., 2012
Mouse	D5	Ciliary body	RT-PCR	Unknown	Bucolo et al., 2012
Monkey, mouse	D2, D3	Ciliary body	RT-PCR, SPET	↓ AH inflow	Billings, Guo, Kung, & Kung, 1993; Bucolo et al., 2012; Platania, Leggio, Drago, Salomone, & Bucolo, 2013
Mouse	D4	Ciliary body	RT-PCR	Unknown	Bucolo et al., 2012
Porcine, dog	D1	Trabecular/meshwork	Autoradiography	↑ cAMP	Karnezis et al., 1989; Elliott et al., 1991
Human	D1	Uveo-sclera	Autoradiography	Control of AH drainage	Cavallotti et al. 1999a
Rabbit	D1, D2	Cornea	Autoradiography	Ion transport	Cavallotti et al. 1999b; Crosson, Beuerman, & Klyce, 1984
Human	D2	Cornea	IHC, WB, RT-PCR	–	Słoniecka et al., 2015

AH = aqueous humor; cAMP = cyclic adenosine monophosphate; IHC = immunohistochemistry; RT-PCR = reverse transcription-polymerase chain reaction; SPET = single-photon emission tomography; WB = western blot.

dominant. In the aqueous humor, the concentration of DA is roughly twice that of NE, while no epinephrine (EPI) has been found, both in rabbits and humans (Figueira et al., 2018). A robust amount of DA was also found in the iris of both rabbits and humans (Figueira et al., 2018). It has been demonstrated that DRs are expressed in a variety of ocular tissues including, among others, retina (Caravaggio et al., 2018), iris ciliary-body (Bucolo et al., 2012), uveo-scleral tissue (Cavallotti, Pescosolido, Pescosolido, & Iannetti, 1999), trabecular meshwork (Karnezis, Tripathi, Dawson, Murphy, & Tripathi, 1989) and cornea (Cavallotti, Pescosolido, Artico, & Feher, 1999) (Table 1). The most important function of DR outside the retina, that is de facto the CNS, is at the ciliary body, the trabecular meshwork and the uveo-scleral tissue, simply because these areas are implicated in the regulation of intraocular pressure (IOP). Physiological IOP values are maintained thanks to a fine tuning between aqueous humor inflow and outflow by these tissues. In particular, production and drainage of aqueous humor take place at the processes of ciliary body and trabecular meshwork/uveoscleral pathway, respectively.

The role of the DA system on IOP regulation has been well documented (Reitsamer & Kiel, 2002); DA modulates ciliary blood flow and aqueous production in a dose-dependent manner with a significant decrease of IOP.

These findings have an important impact on glaucoma that represents one of the leading causes of irreversible blindness affecting more that 60 million people in the world. Glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell death and irreversible loss of peripheral and central visual field usually as consequence of elevated IOP. Elevated eye pressure is the main risk factor for glaucoma, and IOP is determined by the balance between production and drainage of aqueous humor by the ciliary body and outflow pathways, respectively. About 70% of aqueous humor is drained through the conventional (trabecular meshwork) outflow pathway and the rest is removed through the unconventional (uveoscleral) outflow pathway (Fig. 2). A number of classical D2R agonists, including cabergoline, bromocriptine, lergotrile, lisuride, pergolide and cianergoline, have been shown to elicit ocular hypotension in animals and humans (Geyer, Robinson, & Lazar, 1987; Mekki, Hassan, & Turner, 1983; Potter & Burke, 1982; Potter & Shumate, 1987), while D1R agonists, such as ibopamine and fenoldopam, increase IOP in glaucomatous and ocular normotensive patients (Dominguez-Duenas et al., 2016; Piltz et al., 1998; Virno et al., 2013).

In isolated rabbit ciliary epithelium, DA increases passive permeability and active secretion (Green, Hensley, & Lollis, 1979), while H3-inulin dilution measurements of aqueous flow suggest that intracameral DA increases aqueous production in anesthetized rabbits (Green & Elijah, 1981). Another indication that topical DA stimulates aqueous production comes from its ability to accelerate the recovery of IOP from intravenous hypertonic saline in conscious rabbits (Chiou & Chiou, 1983). In contrast to these early studies, subsequent work with ligands for selective DR subtypes suggests that DA has a more complex effect on aqueous production. It has been proposed that aqueous production is stimulated by the activation of D1R and inhibited by the activation of D2R. Recently, selective activation of D2R and D3R has also been shown to decrease aqueous production, most likely by postganglionic, prejunctional inhibition of NE release (Chu, Chu, & Potter, 1999, 2000). Aqueous flow responds to DA in a biphasic manner, increasing at a low infusion rate (dopamine 40 mg/min) and decreasing at a high infusion rate (DA 600 mg/min) (Reitsamer & Kiel, 2002). It is noteworthy that DA at high doses binds to other receptors (e.g. alpha- and beta-adrenoceptors) in addition to DRs. Activation of alpha2 adrenoceptor in addition to the D2R stimulation causes inhibition of NE release, reducing aqueous production as a consequence. This would be offset by the activation of D1R, alpha1, and beta2 adrenoceptors, complicating the mechanisms responsible for the decrease in aqueous flow at high DA concentrations. The above mentioned framework is further complicated by data indicating that D3R stimulation decreases IOP in rabbits (Chu et al., 2000). Consistent with these findings, it has been reported that the DA system plays an important role in the regulation of IOP, and D3R is the key binding site in IOP-lowering effects (Bucolo et al., 2012). In particular, this latter study shows that topical application of 7-OH-DPAT, a D3R preferring agonist, significantly decreases, in a dose-dependent manner, IOP in wild-type (WT) mice both in an ocular normotensive group and in an ocular hypertensive group; pretreatment with U-99194A, a D3 receptor antagonist, reverted 7-OH-DPAT induced ocular hypotension. Therefore, D3R has important implications for glaucoma that represents the most common severe optic neuropathy.

3. Dopamine and the cardiovascular system

Dopamine receptors in the heart and vasculature have been identified and pharmacologically characterized since the 1960s. Currently, DA itself and fenoldopam are approved in the US and EU as drugs supposedly acting on cardiovascular DRs. As pointed out in earlier pharmacological studies, however, as plasma concentrations increase, DA is likely to also act as an adrenergic agonist (at both alpha and beta adrenoceptors)(Goldberg & Rajfer, 1985; Ruffolo Jr., Messick, & Horng, 1984), while fenoldopam, a selective D1R agonist, may also act as an antagonist to alpha adrenoceptors (Martin & Broadley, 1995; Nichols, Ruffolo Jr., & Brooks, 1990). A specific vasodilatory effect of DA was identified at the renal level in the 1960s (McDonald Jr., Goldberg, McNay, & Tuttle Jr., 1964); later, such an effect was attributed to D1-like receptor stimulation, based on the effect of fenoldopam (Hahn, Wardell Jr., Sarau, & Ridley, 1982), leading to the hypothesis that DA produces renal vasodilatation through D1R, which is mainly coupled to adenylyl cyclase through Gs. As mentioned above, earlier studies distinguished only

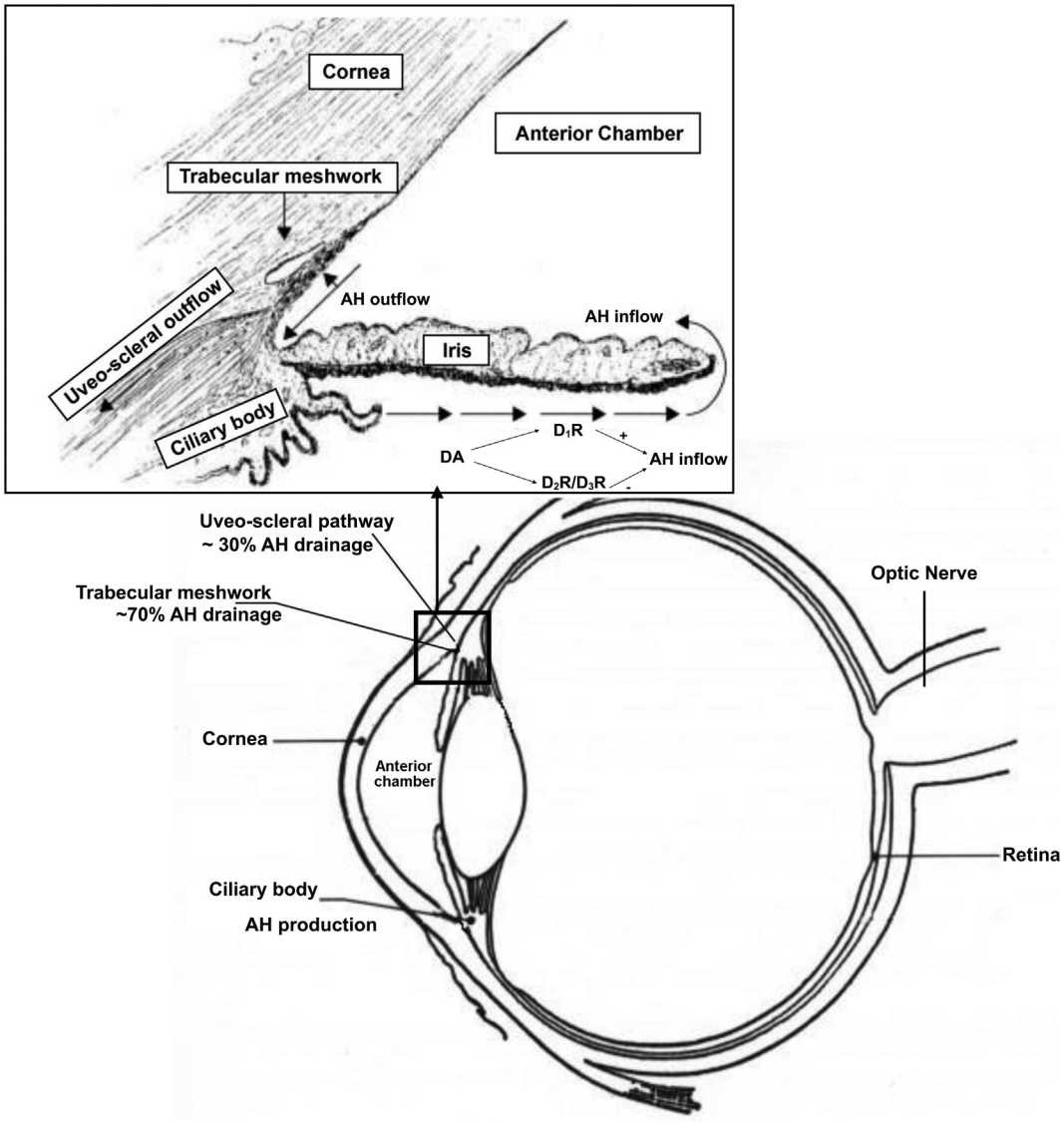

Fig. 2. Schematic illustration showing the production and flow of aqueous humor in the anterior segment of the eye. DA = dopamine; AH = aqueous humor; DR = dopamine receptor.

D1R and D2R subtype receptors, eventually identified as two subfamilies (D1-like: D1R and D5R; D2-like: D2R, D3R and D4R). However, in contrast with D1-like receptors, D2-like receptors mainly signal through Gi, which inhibits adenylyl cyclase and may thereby induce vasoconstriction. In recent years, the molecular characterization of individual DRs has also been paralleled by a more detailed pharmacological characterization, thanks to the availability of some relatively selective ligands, particularly receptor antagonists, at least as investigational agents. This progress, on one hand has produced further insights (i.e., variants of the D2R have been reported to be associated with hypertension), on the other hand could produce novel cardio-vascular drugs with selective DR action.

We do not discuss in detail here DA and DRs in renal sodium handling by the kidney, though this mechanism may exert profound secondary effects on vasculature and blood pressure. In kidneys, DA is synthesized and secreted from proximal tubule cells and decreases sodium transport; alteration of DA signaling has been proposed to play a role in some hypertensive states (Carey, 2001), particularly contributing to salt-sensitive hypertension (Armando, Konkalmatt, Felder, & Jose, 2015). It is interesting that mice with the deletion of aromatic amino acid decarboxylase in the renal proximal tubule show reduced longevity and hypertension (M. Z. Zhang et al., 2011).

3.1. Dopamine and the heart

DA has been used for some time to treat acute heart failure, though the evidence of its beneficial effect is not robust (Hiemstra et al., 2019). More recently, DA infusion has been linked to the pathogenesis of the Takotsubo syndrome (Nakagawa, Fukawa, Tsuji, Nakano, & Kato, 2016). This is an acute condition characterized by marked left ventricular dysfunction in the presence of a nearly-normal coronary angiogram; the prognosis is severe, presenting high mortality, though a recovery may occur within days or weeks (Pelliccia, Kaski, Crea, & Camici, 2017). The Takatsubo syndrome has been linked to toxicity of endogenous cathecholamines, because it is often associated to emotional stressors, supposedly activating the sympathetic nervous system. However, the observation of a Takatsubo case where NE and EPI where in the normal range, while DA was extremely high (following infusion, as a drug-treatment), points to the potential risk associated to DA infusion (Nakagawa et al., 2016). The mechanism of catecholamine toxicity, including DA, has been attributed to potential actions on myocardium and/or coronary microcirculation, but remains largely to be elucidated (Pelliccia et al., 2017).

Several studies have tried to demonstrate DR expression in the heart and correlate it to functional effects of DA itself and/or DR agonists and

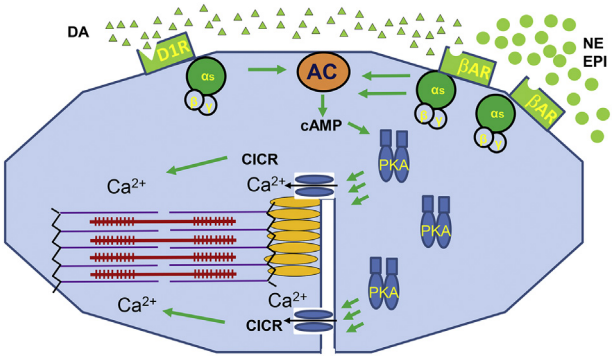

Fig. 3. Schematic illustration showing the potential effect of dopamine (DA) in a cardiomyocyte. Exogenously administered dopamine (DA) leads to activation of DA receptor 1 (D1R) and beta-adrenoceptor (βAR). D1R induces, through Gs (α_s coupling), activation of adenylyl cyclase (AC), with the ensuing increase in cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA); however, a more massive and relevant activation of AC is induced by the activation of βAR, either by exogenous DA or by endogenous norepinephrine (NE) and/or epinephrine (EPI). PKA phosphorylates voltage-dependent L-type Ca2+ channels on tubule T, leading to increased Ca^{2+} conductance and subsequent increase of Ca^{2+}-induced calcium release (CICR) related. Other potential targets of PKA (phospholamban, ryanodine receptor) may play a relevant role, but are not depicted in the figure for clarity. Increased availability of Ca2+ will enhance sarcomere shortening and myocardial contractility.

antagonists. The original paper reporting cloning and characterization of D1R did not detect its mRNA expression in peripheral tissues, presumably because of the assay sensitivity (northern blot) (Dearry et al., 1990). Later, D1R was shown to be expressed in rat myocardium and coronary arteries (Ozono et al., 1996), and subsequently in adult human myocardium (Ozono et al., 1997), both at the protein level, by immunohistochemistry (IHC) and/or western blot (WB), and mRNA level, by in situ amplification, in situ hybridization (ISH) and reverse transcription-polymerase chain reaction (RT-PCR); however, the functional role of D1R remains largely unclear. In rat cardiomyocytes and coronary arteries D1R expression is higher in 4-week old rats and substantially decreases at 8 and 20 weeks (Matsumoto et al., 2000). Consistent with this result, in rabbit ventricular myocytes DA increases L-type calcium current, showing a more pronounced effect in cells from newborns than in those from adults; such an effect is accompanied by D1R mRNA expression that is higher in newborns than in adults (Ding et al., 2008). However, in the presence of SCH-23390, a D1 receptor antagonist, DA is still able to increase L-Type Ca2+ currents, suggesting that most of its action is attributable to beta adrenoceptor stimulation (Ding et al., 2008). D1R protein expression has been also reported by other authors in neonatal rat cardiomyocytes (H. Z. Li et al., 2008). Thus, convergent data show D1R expression in cardiomyocytes across three species, including humans; furthermore, the effect of D1R stimulation by DA itself or by D1R agonists on L-type Ca2+ currents seems consistent with the inotropic effect of DA observable in clinical settings. Considering that D1R is coupled through Gs to adenylyl cyclase, we might be tempted to link this effect to the well-known signaling cyclic adenosine monophosphate (cAMP) - protein kinase A (PKA) -induced L-type Ca2+ channel phosphorylation (Fig. 3) (Bean, Nowycky, & Tsien, 1984; Kameyama, Hofmann, & Trautwein, 1985). However, beta adrenoceptors are also coupled to Gs and are typically responsible for cAMP-PKA activation in cardiomyocytes. Thus, it seems that the functional role of D1R in the mammal myocardium, if any (possibly more relevant in neonates), would be indistinguishable from that of beta adrenoceptors (Fig. 3). This view is further supported by data obtained in rats cardiomyocytes, where DA increases L-Type Ca2+ currents, but its action is blocked by the beta adrenergic antagonist propranolol, (Zhao, Matsuoka, Fujioka, & Noma, 1997), again indicating that the inotropic effect of exogenous DA is largely mediated by beta adrenoceptors (Fig. 3). We also should keep in mind that, while catecholamines released by sympathetic nerve endings and/or adrenal medulla reach concentrations adequate to activate cardiac adrenoceptors, endogenous DA concentrations are generally insufficient to stimulate cardiac DRs. D2R-like receptors in the myocardium have not been firmly demonstrated, though data obtained in D3R null mice suggest that they might modulate extracellular matrix remodeling (through metalloproteinases), and thereby be involved in cardiac fibrosis (Johnson et al., 2013). Studies where cardiac DR expression has been detected at the protein and/or mRNA level are summarized in Table 2.

3.2. Dopamine and the vasculature

Regarding blood vessels, DRs have been found in the aorta, renal, coronary, pulmonary, mesenteric and cerebral arteries of several species, including humans, with a striking non-homogeneous distribution (Amenta, Collier, & Ricci, 1990). Some studies proposed the involvement of DRs in different diseases, such as hypertension, atherosclerosis, diabetes and obesity, suggesting that they may serve as targets in the management of these pathological conditions and of the cardiovascular and metabolic side effects associated with the use of antipsychotics (Scigliano & Ronchetti, 2013). Studies on animal models and humans reported that the stimulation of D2R-like receptors using DA agonists, such as bromocriptine and 7-OH-DPAT, decreases insulin plasma levels and insulin receptor expression in a tissue-specific manner, improves the metabolic profile and decreases the systolic blood pressure (Huang et al., 2011; Kok et al., 2006; Uvnas-Moberg, Ahlenius, Alster, & Hillegaart, 1996), proposing the D2R-like receptors as a potential therapeutic target in diabetes and hypertension. Other studies correlated the increase in blood pressure to the decrease in D1R, D2R and D5R expression in mesenteric arteries (Fu et al., 2014; Ricci et al., 2002).

Table 2
Dopamine receptor expression in heart.

Species	Dopamine receptor subtype	Cell type/area	Protein (assay)	mRNA (assay)	Functional data	Reference
Rabbit	D1	Ventricular myocytes	–	RT-PCR	Increase L-type Ca2+ currents	Ding et al., 2008
Rat	D1	Primary culture cardiomyocytes	WB	–	Proapoptotic	Li et al., 2008
Guinea pig	D3, D4	Ventricle	WB	–	Negative chronotropism inotropism	Gómez Mde et al., 2002
Rat	D1	Cardiomyocytes	IHC	Competitive PCR	–	Matsumoto et al., 2000
Human	D1	Atrial and ventricular myocytes	IHC, WB	–	–	Ozono et al., 1997
Rat	D1	Cardiomyocytes	IHC, immunogold	In situ amplification, RT-PCR	–	Ozono et al., 1996
Rat	D1	Cardiomyocytes	–	RT-PCR	–	Zhang, Qiao, Zhao, & Zhao, 1996

IHC = immunohistochemistry; RT-PCR = reverse transcription-polymerase chain reaction; WT = western blot.

For about two decades (1970s and 1980s), vascular DRs were mainly characterized through functional and/or radioligand binding studies. We do not discuss these data here both for lack of space and because agonists and antagonists, when not specific and selective enough, do not provide the basis for an univocal and unambiguous identification of the receptor isoform (Salomone & Waeber, 2011). More recently (since the 1990s), DR expression in vessels has been analyzed at the mRNA level, by ISH and RT-PCR, and at the protein level, by WB or IHC/immunofluorescence. While mRNA studies do not provide an estimate of the receptor protein in the plasma membrane, they might be useful to get at least an idea of the expressed DR subtype and of the relative amount of different subtypes. In this context, the advantage of mRNA studies is the absolute specificity of the probe/primer sequences, which precisely defines the detection of the mRNA species. In contrast, because of the high homology among DR subtypes within a subfamily (Platania, Salomone, Leggio, Drago, & Bucolo, 2012), antibodies may not well discriminate the different receptor proteins on the cell surface, nor do they with denatured proteins in blotted membranes. Moreover, because the molecular size of DR subtypes is relatively close (D1R, 49 kD; D5R, 53 kD; D2R, 47 kD; D3R, 44 kD; D4R, 41 kD) (Beaulieu & Gainetdinov, 2011), their signal in immunoblots could be, at least in part, superimposed.

Data assessing mRNA and/or protein expression of DRs in vessels seem to converge in showing D1R-like receptors expressed in ECs and D2R-like receptors expressed in prejunctional sympathetic nerve endings; less information is available about vascular smooth muscle cells (VSMCs), suggesting that DRs do not generally reach an expression level comparable to that of endothelium and/or sufficient to be discriminated from those expressed in sympathetic nerve endings, which are very close to VSMCs. Expression data in veins are more scarce; an early study did not detect D1R and D2R mRNA by ISH in rat vena cava, while detecting both receptors in arteries (Kim et al., 1999). Worthy of note, it has been shown that catecholamines are synthesized and released by ECs, based both on mRNA detection (RT-PCR) and immune detection of the synthetic enzymes as well as on measurements of catecholamines released in the culture medium. However, while NE and EPI only were detected in bovine ECs (Sorriento et al., 2012), more recently DA also has been detected in ECs from the porcine pulmonary trunk (Pfeil et al., 2014). A number of functional effects have been so far attributed to D1R-like stimulation in ECs, including endothelium-dependent vasodilatation (Pfeil et al., 2014). Data on D1-signaling in ECs are lacking, therefore, we can only speculate about the potential mechanism(s) involved in D1R-induced vasodilatation, starting from the well-known D1R/Gs/cAMP/PKA axis. Considering that beta-adrenoceptors are typically coupled to Gs, we first consider studies examining the signal-transduction of beta adrenoceptors in ECs. A number of studies, in fact, have shown that beta adrenoceptors, particularly beta2 and beta3, induce endothelium-dependent vasodilatation, and have analyzed their signal-transduction pathway. However, in general, these studies do not show a stimulation of endothelial nitric oxide synthase (eNOS) via cAMP/PKA, but, rather, a PI3K/Akt-dependent increase in S1177 phosphorylation of eNOS, following a paradoxical activation of Gi (Banquet et al., 2011; Figueroa et al., 2009; Isenovic et al., 2002). In the CNS, D2R and D3R are known to inhibit Akt (rather than activating it) through beta-arrestin, while D1R does not signal through Akt (Beaulieu et al., 2007; Beaulieu & Gainetdinov, 2011). Thus, a D1R/Gi/Akt activation of eNOS is not supported by available data. Recently, D1R has been found to signal in the CNS through the activation of the GTP-binding protein Rac1, while D2R may inhibit Rac1 (J. Li et al., 2015; Tu et al., 2019); considering that the Rac1-signaling pathway plays a relevant role in activating eNOS (Sawada, Salomone, Kim, Kwiatkowski, & Liao, 2008), we can speculate that D1R-induced, endothelium-dependent vasodilatation is mediated by Rac1 activation, through the activation of Exchange Proteins Activated by cAMP (EPAC, Fig. 4). Additional experimental data need to be generated to understand the physiological role of DA and DRs in the vascular endothelium,

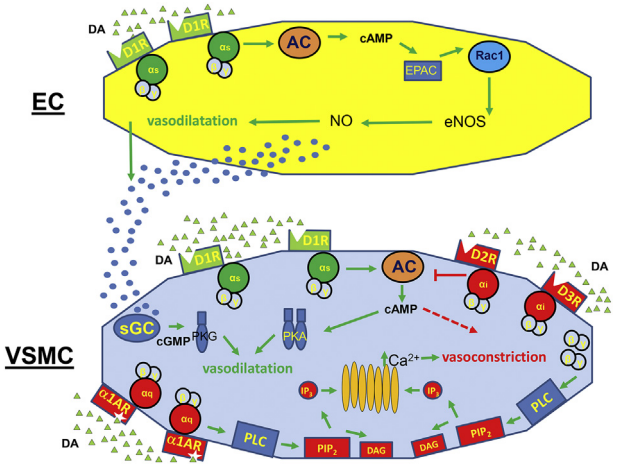

Fig. 4. Schematic illustration showing the potential effect of dopamine (DA) in arteries. DA may lead to the activation of DA receptor 1 (D1R) on endothelial cells (EC) and of D1R, D2R, D3R and alpha1-adrenoceptor (α1AR) in vascular smooth muscle cells (VSMC). Activation of D1R in EC induces, through Gs (α_s coupling), activation of adenylyl cyclase (AC), with ensuing increase in cyclic adenosine monophosphate (cAMP) and activation of Exchange Proteins Activated by cAMP (EPAC); EPAC activates Rac1, which in turn increases the enzymatic activity of endothelial nitric oxide synthase (eNOS), through multiple mechanisms (not depicted in the figure for clarity). Nitric oxide (NO) diffuses into the VSMC, where it stimulates soluble guanylyl cyclase (sGC), which produces cyclic guanosine monophosphate, thereby activating protein kinase G (PKG), which induces VSMC relaxation and vasodilatation. Activation of D1R in VSMC induces, through Gs (α_s coupling), AC activation, with ensuing increase in cAMP and activation of protein kinase A (PKA), which induces vasodilatation; this mechanism might be responsible for the vasodilatory effect of the D1R agonist fenoldopam at the renal level. Activation of D2R and D3R in VSMC induces, through Gi (α_i coupling), inhibition of AC, with ensuing decrease in cAMP and inhibition of downstream events; moreover, Gi $\beta\gamma$ subunits might activate phospholipase C (PLC). A more robust activation of PLC is induced through the stimulation by DA of α1AR, which signals through Gq (α_q coupling). PLC hydrolyzes phosphatidylinositol diphosphate (PIP_2), generating diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3); this latter activates an IP_3-sentive channel (not shown in the figure) located in the sarco-endoplasmic reticulum, with ensuing Ca2+ release, VSMC contraction and vasoconstriction.

considering that also other receptor subtypes, such as D4R, have been proposed to be expressed in ECs, based on the observation that amphetamine induces mRNA expression of tissue factor in human aortic ECs, an effect blocked by the D4R antagonist L-745,870 (Gebhard et al., 2010). In renal arteries D1R, located on VSMC, is generally considered as mediating the vasodilatation induced by fenoldopam, a D1R agonist. However, despite the large amount of studies describing the functional effects of fenoldopam, there is a paucity of data on the expression level of DRs in renal vasculature. Both D1R and D3R have been detected at the protein level (immunoblot) in renal arteries of normotensive and hypertensive rats (Zeng et al., 2004), but the D3R might actually be prejunctional in sympathetic nerve endings, as suggested by others (Amenta et al., 2000). D1R expressed by VSMC supposedly induces vasodilatation through the classical Gs/cAMP/PKA signaling pathway (Fig. 4) (Haynes Jr., Robinson, Saunders, Taylor, & Strada, 1992; Wang, Zhao, & Qin, 1994; Zhu, Zhao, & Zhang, 2000). Studies where vascular DR expression has been detected at the protein and/or mRNA level are summarized in Table 3.

4. Metabolic disorders (diabetes) associated with Parkinson's disease and schizophrenia: role of medications

Alterations in DA transmission have long been associated with PD and schizophrenia (Leggio et al., 2016). Therefore, the first approach to assess the involvement of peripheral DA in insulin secretion and diabetes would logically explore the occurrence of diabetes in PD and schizophrenia patients. However, because most of these patients receive chronic drug treatments (D2R agonists/L-3,4-dihydroxyphenylalanine, L-DOPA for PD, antipsychotics/D2R

Table 3
Dopamine receptor expression in arteries.

Artery/species	Dopamine receptor subtype	Cell type	Protein (assay)	mRNA (assay)	Functional data	Reference
Mesenteric/Rat	D1	–	WB	–	Vasodilatation	Sun, Chen, Wang, Zhou, & Zeng, 2019
Mesenteric/Rat	D1	–	WB	–	Vasodilatation	Fu et al., 2014
Aorta/Rat	D4	Vascular smooth muscle	WB IHC	RT-PCR	Inhibition cell migration (neointima)	Yu et al., 2014
Pulmonary/Human	D1, D5	Endothelial	WB IHC	–	–	Ricci, Mignini, Tomassoni, & Amenta, 2006
Pulmonary/Human	D2, D4	Sympathetic nerve endings	WB IHC	–	–	Ricci et al., 2006
Mesenteric/Rat	D1, D5	Media	IHC	–	–	Ricci et al., 2002
Mesenteric/Rat	D2, D3, D4	Aventitia/Media	IHC	–	–	Ricci et al., 2002
Pial, mesenteric, renal/Rat	D1, D5	Media (smooth muscle)	IHC	–	–	Amenta et al., 2000
Pial, mesenteric, renal/Rat	D2 and D4 (D3 renal only)	Adventitia (sympathetic nerve endings)	IHC	–	–	Amenta et al., 2000
Human (primary cell culture)	D2, D3, D4	HAEC and HUVEC	–	RT-PCR	Inhibition of VWF secretion	Zarei et al., 2006
Mesenteric/Rat	D1 and D3	–	WB	–	Vasodilatation	Zeng et al. 2004
Coronary/Rat	D1	Vascular smoot muscle	IHC	Competitive PCR	–	Matsumoto et al., 2000
Aorta, Carotid, Vertebral/Rat	D1	Media (smooth muscle)	–	ISH	–	Kim et al., 1999
Aorta, Carotid, Vertebral/Rat	D2	Intima, adventitia	–	ISH	–	Kim et al., 1999
Coronary, Renal/Human	D1	–	IHC, WB	–	–	Ozono et al., 1997
Aorta, Pulmonary/Rat	D1	Media (smooth muscle)	–	ISH	–	Jin, Zhang, Zhao, & Zhao, 1997

cAMP = cyclic adenosine monophosphate; HAEC = human aortic endothelial cells; HUVEC = human umbilical vein endothelial cells; IHC = immunohistochemistry; ISH = in situ hybridization; RT-PCR = reverse transcription-polymerase chain reaction; WB = western blot.

antagonists for schizophrenia), gathering data from drug naive patients may not be easy.

A relationship between PD and glucose metabolism derangements, including insulin resistance and type 2 diabetes (T2D) has been repeatedly hypothesized. The general view was that insulin resistance or T2D represent risk factors of PD and may also aggravate its clinical manifestation (Cereda, Barichella, Cassani, Caccialanza, & Pezzoli, 2012; Moroo et al., 1994). Recent evidence from animal studies, showing that high fat diet induces insulin resistance and impairs motor symptoms in a rat model of PD, further support this hypothesis (Sharma & Taliyan, 2018). However, the possibility that clinically overt PD precedes the alterations in glucose homeostasis and/or diabetes should also be taken into account; in fact, a recent report shows that PD patients have higher blood glucose following oral glucose challenge compared to healthy controls, paralleled by lower insulin release (Marques et al., 2018). The underlying mechanism has not yet been explored, but it might be related to an alteration in sympathetic function, because sympathetic neural activity inhibits insulin secretion and also exerts trophic effects on the endocrine pancreas (Kiba, 2004), while evidence is available that sympathetic activity is impaired in PD patients (Hirashima, Yokota, & Hayashi, 1996; Turkka, Juujarvi, & Myllyla, 1987). As regards drug treatments in PD, long term treatment with L-DOPA decreases insulin secretion stimulated by oral glucose in PD patients (Rosati, Maioli, Aiello, Farris, & Agnetti, 1976), while D2R agonists, such as rotigotine, cabergoline, pramipexole and ropinirole do not seem to significantly affect insulin release. In contrast, bromocriptine inhibits glucose-induced insulin secretion (de Leeuw van Weenen et al., 2010), an effect that has been attributed to alpha2-adrenoceptor stimulation in beta-cells (de Leeuw van Weenen et al., 2010); however, it should be noticed that bromocriptine, unlike the D2R agonists mentioned above, acts not only as an agonist on D2R but also as an antagonist on D1R. Bromocriptine, in fact, exerts peculiar actions on insulin release and sensitivity, as further discussed below, which lead to its approval by the FDA for the treatment of T2D. D2R agonists are also used to block prolactin release in hyperprolactinemia syndromes, which secondarily improves insulin sensitivity and metabolic balance; in such conditions, where the stimulation of D2R in pituitary lactotropic cells is the sole determinant of the therapeutic efficacy, cabergoline is more effective than bromocriptine in improving insulin sensitivity (Krysiak & Okopien, 2015).

Schizophrenia (earlier referred to as dementia praecox) was consistently reported to be associated with T2D in studies carried out before the antipsychotic era (Freyberg, Aslanoglou, Shah, & Ballon, 2017). Recent meta-analyses confirm these earlier reports, showing a baseline increased risk for metabolic syndrome at the onset of treatment (Mitchell et al., 2013; Mitchell, Vancampfort, De Herdt, Yu, & De Hert, 2013; Pillinger et al., 2017). Some D2R polymorphisms have been implicated in schizophrenia, and, in some instances, they have been shown to be associated with insulin resistance and/or T2D. For example, the TT genotype of rs6275 and the CC genotype of rs6277 are associated to both schizophrenia and increased fasting blood glucose (Lawford et al., 2016). Areas in the genome that may determine the risk of severe mental illness overlap with areas associated with diabetes or metabolic disorders, in particular the 1q21–42 32 region; many of the genes associated with schizophrenia are expressed in the brain, and include the gene that encodes the D2R (Holt & Mitchell, 2015). These data support the view that the comorbidity of T2D and schizophrenia may be due to D2R alterations occurring simultaneously in the CNS and the endocrine pancreas; in particular, the TT genotype producing higher D2R affinity for DA (Voisey et al., 2010). Impaired glucose tolerance has also been found in non-psychotic, first-degree relatives of schizophrenia patients, further indicating an inheritable phenotype that tracks with risk of psychosis, but is independent of the actual development of a psychotic disorder (Spelman, Walsh, Sharifi, Collins, & Thakore, 2007).

Moreover, data from patients treated with antipsychotics consistently show an increased risk of diabetes; however, typical and atypical antipsychotics show no difference in this respect, both increasing the risk of diabetes by a factor of 3 (Rajkumar et al., 2017). Considering that typical and atypical antipsychotics significantly differ in their pharmacology (the former acting strongly on D2R, the latter acting weakly on D2R), the simple correlation between genetic and/or pharmacological blockade of D2R and diabetes becomes difficult to accept. For example, clozapine and olanzapine produce the highest risk of metabolic disorders, but are drugs with limited D2R antagonism, compared to typical antipsychotics. Once we admitt that a correlation between

disturbances of DA transmission and diabetes exists, the mechanisms to be considered include both central and peripheral scenarios, i.e. mechanisms affecting the regulation of food intake and energy expenditure in the CNS, versus mechanisms affecting peripheral control of hormone secretion (particularly in the endocrine pancreas) and of tissue energy storage and consumption. These two scenarios may also be, in part, superimposed, when considering, for instance, that genetic alterations of D2R would affect all somatic cells expressing this receptor subtype (i.e. neurons as well as cells in pancreatic islets), while pharmacological antagonism by drug treatment would block D2R in the CNS as well as in peripheral cells. Among central mechanisms, many have been proposed and studied, including dysregulation of the hypothalamus-pituitary axis, with particular regard to prolactin, a powerful hormone regulator of systemic glucose homeostasis (Lopez Vicchi et al., 2016). DA secreted by hypothalamic nuclei into the portal system inhibits prolactin secretion from the pituitary gland, mainly through D2R. Other studies reported that decreased D2R expression in some CNS areas is associated with increased feeding motivation, food intake and development of overweight states (Palmiter, 2007; Wang et al., 2001). In some hypothalamic regions, such as the suprachiasmatic nucleus, DA and D2R signaling regulate the circadian rhythms responsible for metabolic control (Barandas, Landgraf, McCarthy, & Welsh, 2015; Landgraf et al., 2016). Finally, a number of indirect mechanisms associated with dysregulated DA neurotransmission in the CNS, including reduced locomotor activity and/or reduced thermogenesis can be taken into account. The detailed role of DA transmission in CNS mechanisms regulating energy balance, insulin release and sensitivity, potentially involved in diabetes, is beyond the scope of this review and will not be further discussed.

We will discuss below the available evidence on DA in the endocrine pancreas, but it is worthy of mention that DRs are also found in adipocytes, where they regulate adiponectin levels; this points to a putative impact of D2R/D3R genetic polymorphisms and/or pharmacological blockade by antipsychotics on metabolic disturbances occurring in schizophrenia patients (Borcherding et al., 2011).

5. Dopamine in the endocrine pancreas

Studies have sought to determine the effect of intravenous (i.v.) DA infusion on insulin release in humans; the results are somewhat conflicting. In some studies, DA infusion has increased insulin secretion in both healthy and T2D individuals (Contreras et al., 2008; Ruttimann, Schutz, Jequier, Lemarchand, & Chiolero, 1991); in contrast, in a recent study, where a hyperglycemic clamp protocol was carried out, DA infusion decreased insulin secretion (Underland, Mark, Katikaneni, & Heptulla, 2018); this effect could be related to alpha-2 adrenoceptor activation. Interestingly, in the absence of DA infusion, there was an inverse correlation between C-peptide and DA plasma levels (Tomaschitz et al., 2012), suggesting that DA in the low-range, basal concentration, inhibits insulin secretion. These inconsistencies may be accounted for by the different levels of DA in plasma and, subsequently, in the islets, depending on the applied infusion rates. As mentioned above, in the absence of an exogenous supply (i.e. i.v. infusion), the plasma DA concentration is close to 0.1 nmol/L (Goldstein & Holmes, 2008), which is far below its K_D for DRs (Marcellino, Kehr, Agnati, & Fuxe, 2012), and therefore unlikely to exert any detectable biological effect attributable to DR stimulation. In contrast, DA infusion produces a number of effects, some of which represent the rationale for its use in shock, where it sustains heart activity, blood pressure and renal blood flow (Loeb, Winslow, Rahimtoola, Rosen, & Gunnar, 1971). However, as mentioned above, such effects are, at least in part, attributable to alpha- and beta-adrenoceptors stimulation (Itoh, Furman, & Gerich, 1982), because the therapeutic plasma concentration attains levels compatible with DA affinity for those receptors (Goldberg & Rajfer, 1985). Similarly, the effects of DA infusion on insulin release might be mediated, at least in part, by alpha- and beta-adrenoceptors. In fact, considering that adrenoceptors are also present in the islets, DA infusion would exert complex effects, resulting from stimulation of both DRs and adrenoceptors. The adrenoceptors involvement in the decrease of insulin secretion following DA infusion is consistent with the observation that NE- and EPI-deficient mice (DA beta-hydroxylase null mice) are hyperinsulinemic (Ste Marie & Palmiter, 2003). The interpretation of the effects of DA infusion on insulin secretion is further complicated by the paracrine control exerted by the different cell types in the islet, as discussed below.

DA acts as an autocrine or paracrine negative regulator of glucose-stimulated insulin secretion. Pancreatic beta cells express D2R (Rubi et al., 2005; Simpson et al., 2012) as well as the vesicular monoamine transporter 2 (VMAT2), responsible for vesicular DA loading and storage (Anlauf et al., 2003). Recently, an extensive proteomic analysis of the pancreas in different mouse strains, revealed that CAST mice, produce elevated DA levels in islets, which suppress insulin secretion (Mitok et al., 2018). The authors identified putative pathways by weighted gene co-expression network analysis of the proteome data. Tyrosine hydroxylase (TH), the key enzyme in catecholamine synthesis, appears ~70-fold higher in islets from CAST and PWK mice compared to other strains. Further IHC analyses indicated that this difference arises mostly from beta cells; i.e., in mouse, beta cells are the main cells expressing TH. This finding suggests that, at least in some mouse strains, catecholamines produced and secreted by beta cells within the islet may represent an additional regulatory mechanism for insulin secretion. The observation that D2R null mice exhibit high fasting glucose and reduced insulin secretion following glucose challenge suggests that D2R stimulation modulates insulin release (Garcia-Tornadu et al., 2010), a notion confirmed by in vitro experiments, where in wild-type islets cabergoline (a D2R agonist) inhibits glucose-stimulated insulin release, an effect blocked by a D2R, but not a D1R, antagonist that is not present in D2R null mice (Garcia-Tornadu et al., 2010). However, data obtained in INS-IE cells, a rat pancreatic beta cell-derived cell line, showed that also bromocriptine, a drug acting as a D2R agonist and D1R antagonist, diminishes glucose-stimulated insulin secretion, similarly to DA (Freyberg et al., 2017); this latter finding may be hard to reconcile, considering that D1R exerts an effect (possibly autocrine, see below) opposite to D2R. Analysis of enzymes involved in catecholamine metabolism leads to the conclusion that DA is the prevalent catecholamine produced in the islets, since DA β-hydroxylase and phenylethanolamine *N*-methyltransferase (responsible for the synthesis of NE from DA and EPI from NE, respectively) have not been detected, indicating that DA produced in the islets does not undergo subsequent transformation to NE and EPI (Mitok et al., 2018). Finally, direct measurements of DA further confirmed that its levels correlate with the content of TH (Mitok et al., 2018). Given that in vitro studies have shown that incubation with DA suppresses insulin secretion from mouse and human islets (Garcia-Tornadu et al., 2010; Rubi et al., 2005; Ustione & Piston, 2012), pancreatic islets appear as an exceptional site outside the CNS, where DA is synthesized and accumulated and, when released, may affect insulin secretion.

Most available data have been obtained, so far, from in vitro experiments carried out on islets, which cannot discriminate in detail which DR subtype/cell type is responsible for a given effect. A recent single-cell transcriptome study, by identifying human islet cell signatures, has shown that D2Rs are much more abundant in delta cells than in alpha or beta cells (Lawlor et al., 2017). Taken together with the evidence of inhibition of insulin secretion by exogenous or endogenous DA, this study may help to formulate a simple hypothesis, where DA, released from beta cells, stimulates D2Rs in delta cells, leading to inhibition of somatostatin (SST) secretion, thereby relieving SST-mediated inhibition on insulin secretion from beta cells (Fig. 5). It has been proposed that DA may act in an autocrine manner on DRs on the surface of the beta cells to inhibit insulin secretion (Garcia-Tornadu et al., 2010; Rubi et al., 2005; Ustione & Piston, 2012). However, the recent finding showing much more (about 100-fold) abundant D2R on delta cells than on beta cells (Chen et al., 2014; Lawlor et al., 2017) supports

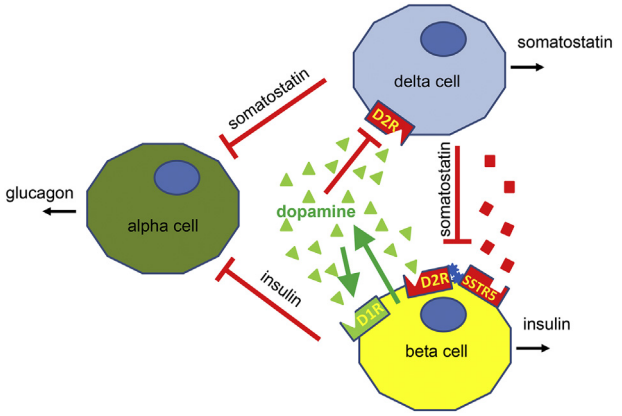

Fig. 5. Proposed autocrine and paracrine mechanisms of dopamine signaling, modulating insulin and somatostatin release in the endocrine pancreas. Dopamine is released by beta cell and activates dopamine receptor 1 and 2 (D1R and D2R), expressed in the membrane of beta cells (autocrine mechanism) as well as D2R expressed by delta cells (paracrine mechanism). In beta cells, the activation of D1R stimulates insulin release (green arrow), while activation of D2R inhibits insulin release, possibly through the formation of heterodimers with somatostatin receptor 5 (SSTR5). In delta cells, activation of D2R inhibits somatostatin release (red bar). Because few or no data are available on dopamine signaling in alpha cells, it has not been considered in the figure; only the well-known inhibitory effects of both insulin and SST on alfa cells are reported, indicated by the red bars.

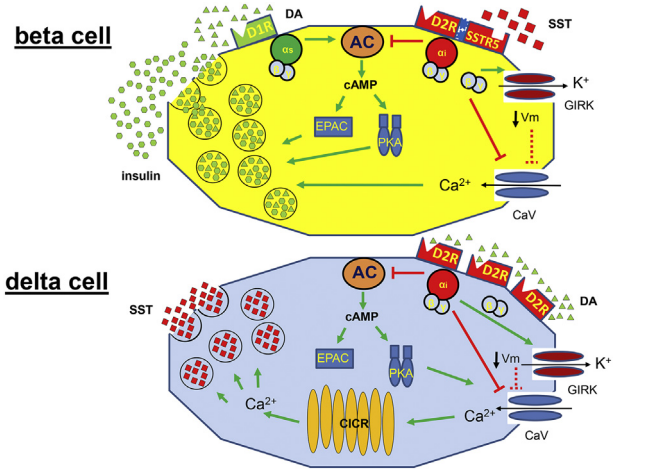

Fig. 6. Potential cellular mechanisms underlying the putative autocrine and paracrine effects of dopamine (DA) in beta and delta pancreatic cells. In beta cells, activation of DA receptor 1 (D1R) induces, through Gs (α_s coupling), the stimulation of adenylyl cyclase (AC), with the ensuing increase in cyclic adenosine monophosphate (cAMP). An increase in cAMP activates protein kinase A (PKA) and other mechanisms, such as Exchange Proteins Activated by cAMP (EPAC), which regulate cytockeletal proteins and modulate insulin secretion. Activation of D2R, somatostatin receptor 5 (SSTR5) and/or of their heterodimers, induces, through Gi (α_i coupling), inhibition of AC, with ensuing decrease in cAMP and inhibition of downstream events. Furthermore, Gi transduction releases βγ subunits, which directly activate K^+ channels (GIRK, G protein-coupled inwardly-rectifying potassium channels) and inhibit different classes of voltage-gated Ca^{2+} channels (CaV); activation of GIRK produces membrane hyperpolarization (↓Vm), which further inhibits CaV activation. The ensuing reduction of Ca^{2+} entry inhibits insulin release. In delta cells, somatostatin release occurs mostly through a Ca^{2+}-induced calcium release (CICR) related mechanism. Activation of D2R induces, through Gi (α_i coupling), inhibition of AC, with ensuing decrease in cAMP and inhibition of PKA and other downstream targets. PKA may phosphorylate CaV, leading to increased Ca^{2+} conductance and subsequent increase of CICR. On the other hand, Gi transduction releases βγ subunits, which directly activate GIRK and inhibit CaV; activation of GIRK produces membrane hyperpolarization (↓Vm), which further inhibits CaV activation. The ensuing reduction of Ca^{2+} entry decreases CICR and inhibits somatostatin release.

a paracrine mechanism, where DA released from beta cells mainly inhibits SST release, which, in turn, increases insulin release. Indeed, DA has been shown to inhibit SST secretion in rat islets, in vitro (Itoh et al., 1982).

The autocrine action of DA in beta cells should be re-examined, also taking into account that DRs and SSTRs are able to form heterodimers (Rocheville et al., 2000), as discussed above. To the best of our knowledge, the interaction between these two receptors firmly demonstrated in the CNS (Rocheville et al., 2000), has not yet been studied in islet cells, presumably because it is technically more challenging. However, considering that the expression of SSTRs and DRs in the beta cell membrane is well established, we may hypothesize that they are capable of forming heterodimers, which would represent a mechanism by which SST modulates the response of beta cell to DR stimulation. In a basal, low glucose condition, DA subnanomolar concentrations, unable per se to activate monomeric/homomeric D2R, might bind and activate D2R/SSTR5 heteromers (Rocheville et al., 2000), which inhibit insulin secretion. After a meal, plasma glucose concentrations increase sufficiently to be taken up inside the beta cell by GLUT2; glycolysis increases ATP that activates sulfonylurea receptor 1, thereby inhibiting K^+ATP channels, which produces cell depolarization, opening of voltage-dependent Ca^{2+}channels and increase in cytosolic Ca^{2+} concentration. Following these events, the exocytosis of insulin vesicles takes place. DA has been shown to be stored in insulin granules via VMAT2 (Raffo et al., 2008; Saisho et al., 2008), which results in co-secretion of DA with insulin in response to a stimulus. DA secretion by beta cells might then stimulate D2R receptors on delta cells, leading to a profound inhibition of SST secretion, which removes the inhibition on insulin secretion exerted by both SST and DA (Fig. 5). In this context, DA would also stimulate insulin release from beta cells through D1R, with an autocrine feed-forward mechanism. Although such a simple feedback mechanism may adequately support the paracrine interaction between beta and delta cells, we do not have detailed information on how D2R stimulation inhibits SST secretion. SST is released by a calcium-induced calcium release (CICR)-dependent mechanism (Q. Zhang et al., 2007), while D2R activation can reduce calcium influx through voltage-dependent calcium channels, possibly also by inducing hyperpolarization of the membrane potential (A. K. Lee, 1996). Thus, reduction of CICR and/or other D2R-dependent events, such as reduction of cAMP production or protein kinase C activity, supposedly decrease SST secretion (Fig. 6). Beta cells seem to express mostly D1R (Chen et al., 2014; Lawlor et al., 2017), but D2R is expressed too (Rubi et al., 2005; Simpson et al., 2012); stimulation of D1R mainly activates adenylyl cyclase through Gs, increasing cAMP production and protein kinase activation (Beaulieu & Gainetdinov, 2011), which, supposedly should increase insulin secretion (Wan et al., 2004) (Fig. 6). A potential role for D2R and D3R expressed by beta cells in inhibiting glucose-induced insulin release has been very recently reproposed, based on the finding that L-DOPA is taken up by beta cells to establish intracellular DA stores and that glucose enhances L-DOPA uptake (Farino et al., 2019). In the same study, D2R- or D3R-null mice showed reduced DA secretion during glucose stimulation. Considering that also selective deletion of D2R in beta cells induces marked postprandial hyperinsulinemia in mice, the authors proposed that DA released by beta cells might exert an autocrine effect through D2R and D3R (Farino et al., 2019). However, it should be pointed out that, in this study (Farino et al., 2019), the inhibition of insulin release in vitro was obtained following exposure to L-DOPA concentrations >30 μM, i.e. about 300-fold higher than those achievable in vivo after a meal (Goldstein et al., 1999; Goldstein, Eisenhofer, & Kopin, 2003). The D2R might have an additional role, in view of the capability to form heterodimers with SSTR5 (Rocheville et al., 2000). Pancreatic beta cells express SSTR2 and SSTR5 receptors, but when challenged with selective agonists, only SSTR5 stimulation inhibits insulin release (Zambre et al., 1999). Thus, if this view is correct: i) DA released by beta cells (i.e. in a autocrine way) hardly inhibits insulin secretion, because the presence of abundant D1R would rather stimulate it; ii) inhibition of insulin secretion by DA, observed in in vitro islets, can hardly be explained on the basis of a single receptor/single cell type, because both D1R in beta cells and D2R in delta cells (by blocking SST secretion) would increase insulin release; iii) a potential

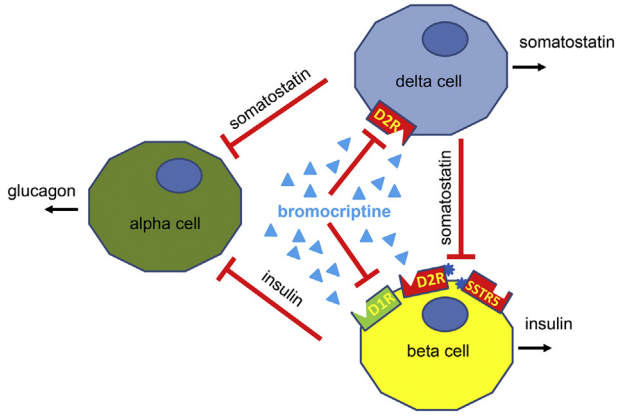

Fig. 7. Bromocriptine activates dopamine receptor 2 (D2R, agonist), expressed on the membrane of both beta and delta cells, while it inhibits dopamine receptor 1 (D1R, antagonist), expressed on the membrane of beta cell; these two actions supposedly inhibit both insulin release from beta cell and somatostatin release from delta cells, as indicated by the red bars. The activation of D2R on beta cell by bromocriptine might further inhibit insulin release through the formation of heterodimers with somatostatin receptor 5 (SSTR5); however, the inhibition of somatostatin release on delta cell would reduce somatostatin release and reduce the possibility of SSTR5 activation.

interplay between DR subtypes and/or between DRs and SSTRs (formation of heteromers) adds complexity to the system, where the cell response would vary according to the presence of DA, SST, or both; iv) a ligand such as bromocriptine, endowed with both D1R (antagonistic) and D2R (agonistic) actions may exert complex effects, resulting from the integration of direct effects on beta cells and paracrine effects from delta cells (Figs. 5 and 6).

6. Therapeutic implications in type 2 diabetes

In general, achieving optimal glycemic control in patients with diabetes is crucial. However, it is estimated that only 50% of adults with any type of diabetes achieve optimal glycemic control with current management. Therefore, there is an unmet medical need for effective and safe medications that can improve the management of diabetes and reduce complications. Preclinical and clinical mechanistic studies conducted on bromocriptine suggests that this pharmacological treatment improves glycemic control in T2D patients by improving glucose disposal and insulin sensitivity. Clinical evidence of safety and efficacy of bromocriptine was generated from randomized, double-blind, placebo-controlled clinical trials in a total of 3723 T2D patients and was based on previous preclinical data (Chamarthi et al., 2015; Gaziano et al., 2010; Scislowski et al., 1999). On this basis, the FDA approved bromocriptine for the treatment of T2D, even though the precise mechanism of action is still unclear at the molecular and cellular level. Bromocriptine acts as a D2R agonist in delta cells, leading to inhibition of SST secretion, thereby relieving SST-mediated inhibition of insulin secretion from beta cells (Fig. 7); at the same time, bromocriptine can act as an antagonist on D1R in beta cells, attenuating insulin release (Fig. 7). Therefore, it seems that bromocriptine is able to create a fine tuning of insulin release, which is useful in T2D patients. The formation of heterodimers between D2R and SST5R on beta cells could have further implications on the regulation of insulin release elicited by DR ligands. It is interesting to note that the leading role of SST in the paracrine regulation of insulin and incretin levels has recently lead to the development of SST5R antagonists as potential drug treatments for T2D (Farb et al., 2017).

7. Concluding remarks

Available data from recent findings indicate that DA plays significant regulatory roles outside the CNS, in several tissues, including the eye, cardiovascular system and endocrine pancreas. DA is produced and released in the anterior segment of the eye, in the vascular endothelium and in the endocrine pancreas and acts on DRs, which are expressed in these tissues. However, when exogenously administered, DA concentrations reach levels sufficient to stimulate alpha and beta adrenoceptors, and such a phenomenon sustains a number of effects, observed both in experimental and clinical settings, particularly in the cardiovascular system. At the cell level, the stimulatory or inhibitory effect of DA signaling is not only influenced by integration with other receptor-signaling pathways, but may also derive from direct interaction between distinct GCPRs, which generate heteromers. Thus, endogenous DA is likely to modulate physiologic functions, while systemically administered drugs acting on DRs might exert unwanted effects at these sites, with potential adverse reactions. Finally, understanding the peripheral effects mediated by DRs could provide pharmacological targets and tools for treating conditions such as glaucoma, cardiovascular diseases and diabetes.

Declarations of Competing Interest

The authors declare that there are no conflicts of interest.

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