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Review

Diabetes and hypertension: Pivotal involvement of purinergic signaling

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ABSTRACT

Diabetes mellitus (DM) and hypertension are highly prevalent worldwide health problems and frequently associated with severe clinical complications, such as diabetic cardiomyopathy, nephropathy, retinopathy, neuropathy, stroke, and cardiac arrhythmia, among others. Despite all existing research results and reasonable speculations, knowledge about the role of purinergic system in individuals with DM and hypertension remains restricted. Purinergic signaling accounts for a complex network of receptors and extracellular enzymes responsible for the recognition and degradation of extracellular nucleotides and adenosine. The main components of this system that will be presented in this review are: P1 and P2 receptors and the enzymatic cascade composed by CD39 (NTPDase; with ATP and ADP as a substrate), CD73 (5′-nucleotidase; with AMP as a substrate), and adenosine deaminase (ADA; with adenosine as a substrate). The purinergic system has recently emerged as a central player in several physiopathological conditions, particularly those linked to inflammatory responses such as diabetes and hypertension. Therefore, the present review focuses on changes in both purinergic P1 and P2 receptor expression as well as the activities of CD39, CD73, and ADA in diabetes and hypertension conditions. It can be postulated that the manipulation of the purinergic axis at different levels can prevent or exacerbate the insurgency and evolution of diabetes and hypertension working as a compensatory mechanism.

Abbreviations: Ado, Adenosine; ADP, adenosine 5′-diphosphate; AMP, adenosine 5′-monophosphate; ATP, adenosine 5′-triphosphate; ADA, adenosine deaminase; APs, alkaline phosphatases; AMPK, AMP-activated protein kinase; AngII, angiotensin-II; APCs, antigen presenting cells; BFR, blood flow restriction; BP, blood pressure; CNS, central nervous system; CGA, chlorogenic acid; cAMP, cyclic adenosine 5′-monophosphate; DCs, dendritic cells; DM, diabetes mellitus; DAG, diacylglycerol; Ap3A, diadenosine triphosphate; DBP, diastolic blood pressure; 5′-NT;CD73, ecto-5′-nucleotidase; E-NTPDase, ecto-nucleoside triphosphate diphosphohydrolase; E-NPP, ecto-nucleotide pyrophosphatase/phosphodiesterase; ER, endoplasmatic reticulum; eNOS, endothelial nitric oxide synthase; NTPDase1/CD39, E-NTPDase family; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; HbA1c, glycosylated hemoglobin; GPCRs, G-protein-coupled receptors; HIAE, high intensity aerobic; HIIT, high-intensity intermittent training; HIF-1α, hypoxia-inducible factor-1α; Ino, inosine; IRS-1, insulin receptor substrate 1; IL, interleukin; L-NAME, L-NG-nitroarginine methyl ester; LIAE, low intensity aerobic exercise; $VO_{2máx}$, maximal oxygen uptake; mRNA, messenger RNA; MICT, moderate intensity continuous training; DAMP, molecular pattern associated with damage; MSNA, muscle sympathetic nerve activity; NO, nitric oxide; NOS, nitric oxide synthase; NLRP3, NLR family pyrin domain containing 3; NOD-mice, Non-obese diabetic mice; NF-κB, nuclear factor kappa B; NFAT, nuclear factor of activated T-cells; PBMCs, peripheral blood mononuclear cells; PAP, prostatic acid phosphatase; PKA, protein kinase A; PNP, purine nucleoside phosphorylase; P2X, purinergic ionotropic receptor family 2; P2Y, purinergic metabotropic receptor family 2; P1, purinergic receptors family 1; TReg, regulatory T cells; STAT3, signal transducer and activator of transcription 3; SIRT1, Sirtuin 1; SHR, spontaneously hypertensive rat; SIT, sprint interval training; STZ, streptozotocin; SBP, systolic blood pressure; TNAP, tissue-nonspecific alkaline phosphatase; TGF-β1, transforming growth factor-beta 1; TXA2, thromboxane A2; TNF-α, tumor necrosis factor α; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; Up4A, uridine adenosine tetraphosphate; UDP, uridine diphosphate; UTP, uridine-5′-triphosphate; VEGF, vascular endothelial growth factor.

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1. Introduction

In the past months, the world has been fighting a difficult pandemic of COVID-19. This disease is a severe acute respiratory syndrome caused by coronavirus SARS-CoV-2. Although several studies have revealed that diabetes (DM) and hypertension are major risk factors for complications and death from COVID-19, it is still unclear whose are the mechanisms related to this condition [1–4]. This scenario shows how important it is to better understand the impacts of DM and hypertension on the whole body, especially when they occur associated with other diseases. Indeed, much more research on these specific topics is required.

DM is a metabolic disease, characterized by chronic hyperglycemia, which induces macro and microvascular dysfunction in the heart, kidney, and retinal and peripheral vasculature that contributes to the increased morbidity and mortality in diabetic individuals [5]. Hypertension is recognized by sets of physiological abnormalities that involve varying degrees of cardiac output, peripheral resistance, cardiopulmonary blood volume, sympathetic neural activity, intravascular volume, renin production, and aldosterone secretion [6]. These dysfunctions are associated with the high expression of angiotensin converting enzyme-2, a fact that also makes DM and hypertensive patients more vulnerable to the risk of severe infection by SARS-CoV-2 [3–7].

The purinergic system is well known to orchestrate the interaction between extracellular nucleotides and adenosine (Ado) in an array of cell–cell communications [8]. Purinergic signaling is a multistep coordinated cascade that includes: (i) nucleotide and nucleoside metabolism; (ii) nucleotide and nucleoside binding to selective P1 or P2 receptor families; and (iii) nucleotide breakdown by membrane-bound and soluble nucleotidases and extracellular Ado inactivation via adenosine deaminase (ADA) [8–10].

Purinergic signaling also regulates immune cell function by modulating the synthesis and release of various cytokines such as interleukin (IL)-1β and IL-18 as part of inflammasome activation [11–13]. Abnormal or excessive stimulation of this intricate paracrine system can be pro- or anti-inflammatory, and it is also linked to necrosis and apoptosis during DM disease [14–16].

2. Purinergic system

2.1. Purinergic signaling: outline and relevance

A large body of evidence supports the pivotal role of purinergic signaling and its components, i.e., signaling molecules, enzymes, and receptors, in several diseases, including cancer [17–21]; inflammatory diseases [22–24]; cardiovascular-related diseases such as hypertension, ischemia, and atherosclerosis [25–27]; psychiatric and neurodegenerative diseases [28–32]; and diabetes [14,16,33–37], among others [38–40]. The purinergic signaling pathway constitutes a ubiquitous system of cell–cell communication and is expressed in almost every cell type [41]. Moreover, research in the field of purinergic signaling has exponentially advanced since the first published studies in the 1970s, and thus the potential role of this system is being explored in the regulation of many other biological functions such as inflammatory responses [12,42–44].

Communication between the purinergic system components is mainly executed by extracellular adenine nucleotides and nucleosides (Fig. 1). These mediators participate in a wide range of physiological processes, including energy metabolism, neurotransmission, vascular integrity, and immune responses [45–47]. Adenosine 5′-triphosphate (ATP), the main energy currency utilized by cells, acts as an important neuromodulator, neurotransmitter, and as a cotransmitter with acetylcholine, dopamine, gamma-aminobutyric acid (GABA), glutamate, and noradrenaline in the brain [48,49]. While ATP acts fundamentally as an excitatory neurotransmitter, Ado, the main metabolite of ATP degradation, generally presents antagonist neuromodulatory effects acting primarily in neuroprotection [49,50].

Extracellular ATP and its breakdown product Ado are also well-known mediators of inflammatory responses. ATP generally functions as a pro-inflammatory molecule while Ado is recognized as an anti-inflammatory agent [12,22,23,45,51]. ATP induces the attraction and

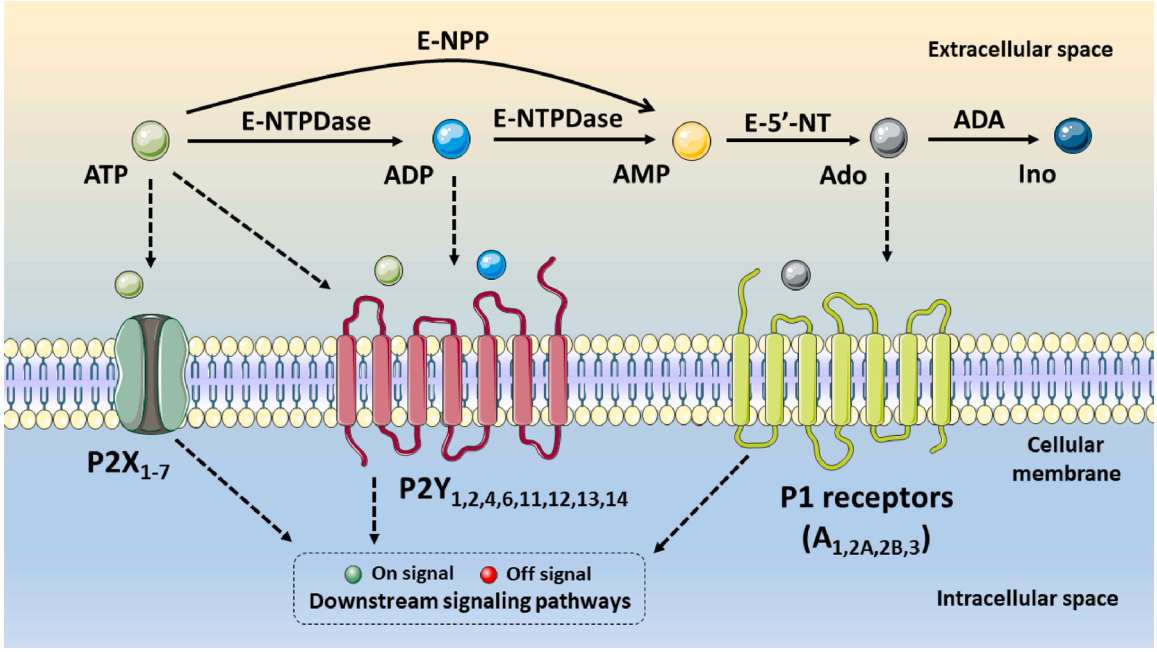

Fig. 1. Overview of the purinergic signaling cascade.
The purinergic pathway is comprised by several purine-hydrolyzing enzymes expressed on the cell surface, generally known as ectoenzymes, including E-NTPDase, E-NPP and E-5′-NT, that sequentially degrade nucleotides in a series of coordinated reactions. The resulting nucleoside adenosine (Ado) can be subsequently converted to inosine (Ino) by adenosine deaminase (ADA). Signaling molecules bind to ionotropic P2X receptors and metabotropic P2Y receptors depending on the affinity of each receptor for their nucleotide agonists. The four subtypes of P1 types have affinity to adenosine and are all G-protein-coupled receptors (GPCRs). The binding of the purinergic mediators to their specific receptors on the cell surface can turn on or off downstream signaling cascades leading to different cellular outcomes. Source: Authors artwork.

recruitment of antigen presenting cells (APCs) and induces pro-inflammatory responses while Ado acts in immunosuppression, limiting the proliferation and activation of effector T cells [52]. Besides, purinergic signaling is involved in platelet homeostasis: While adenosine 5′-diphosphate (ADP) stimulates platelet aggregation, Ado prevents this process [53].

2.2. Nucleotide- and nucleoside-converting enzymes

The levels of adenine nucleotides and nucleosides are regulated by membrane-bound and soluble enzymes. These include a) the family of ecto-nucleoside triphosphate diphosphohydrolase (E-NTPDase) enzymes; b) the family of ecto-nucleotide pyrophosphatase/phosphodiesterase (E-NPP); c) ecto-5′-nucleotidase/CD73; d) alkaline phosphatases (APs), including tissue-nonspecific alkaline phosphatase (TNAP) and prostatic acid phosphatase (PAP); and e) enzymes responsible for the breakdown of Ado such as ADA and purine nucleoside phosphorylase (PNP) [54,55]. Increasing evidence has demonstrated the central role of purine-degrading enzymes in many pathological contexts, including inflammation-related conditions [22].

NTPDases are metalloenzymes expressed in almost every tissue [10]. They require Mg^{2+} and Ca^{2+} as cofactors and are responsible for the hydrolysis of tri- and diphosphate nucleotides into mononucleotides and inorganic phosphate. The NTPDase family is encoded by eight genes; the enzymes differ in cellular and tissue localization and substrate specificity [10]. NTPDase1, NTPDase2, NTPDase3, and NTPDase8 are membrane-bound extracellular enzymes; NTPDase5 and NTPDase6 are found within the cytoplasm; and NTPDase4 and NTPDase7 are intracellular enzymes, which face the lumen of cytoplasmic organelles [55].

The first known member of the E-NTPDase family (NTPDase1/CD39) has been widely studied; it has equal affinity for ATP and ADP. Other NTPDases have different substrate preferences and can hydrolyze a variety of nucleoside di- and triphosphates, including uridine 5′-triphosphate (UTP) and uridine diphosphate (UDP). Besides, all membrane-bound NTPDases are known to degrade ATP more rapidly than ADP [10]. NTPDase1 is mainly expressed on immune cells, such as lymphocytes and dendritic cells (DCs), smooth muscle cells, and vascular endothelial cells, and is involved in the mediation of inflammatory responses [54,56,57]. NTPDase2 has an important role in vascular integrity and may facilitate platelet aggregation by promoting ADP-mediated stimulation of P2Y purinoceptor 1 and 12 (P2Y1 and P2Y12, respectively) [55].

The NPP family comprises seven structurally related enzymes (NPP1–7), which hydrolyze triphosphate nucleotides (such as ATP) into monophosphate nucleotides (such as adenosine 5′-monophosphate [AMP]) and pyrophosphates [55]. However, only three members of this family of enzymes (NPP1, NPP2, and NPP3) are relevant in the context of the purinergic signaling, especially NPP1 and NPP3, which hydrolyze ATP at comparable rates [54]. NPP4, although unable to hydrolyze nucleotides, participates in the conversion of diadenosine triphosphate (Ap3A), a platelet component released during platelet aggregation, into ADP and AMP, an action that increases platelet aggregation [58]. APs are ubiquitously found in several organisms and also require metal ions (Mg^{2+} and Zn^{2+}) for enzymatic activity. These enzymes have a broad substrate specificity for compounds containing phosphate, including adenine nucleotides, pyrophosphates, and inorganic polyphosphates [10,54,55].

Seven human 5′-nucleotidases have been identified: one is a plasma membrane-bound enzyme, one is located in the mitochondrial matrix, and five are present in the cytosol [54]. Ecto-5′-nucleotidase/CD73 is a Zn^{2+}-binding protein [10] with implications in several (patho)physiological processes, including immunomodulation and inflammation, and the regulation of purinergic signaling cascade [55]. The primary function of this enzyme is the generation of the extracellular nucleoside Ado from extracellular AMP [10]. 5′-Nucleotidase is highly expressed in tissues such as the kidney, brain, and colon, and less distributed in the liver, heart, and lungs [59]. This enzyme is also abundantly found in the endothelium and platelets, but only found in some subpopulations of immune cells [26,55,60].

At the end of the purinergic cascade, there are two ADA isozymes in humans, ADA1 and ADA2, which regulate Ado levels [54]. Considering the relevance in the purinergic cascade, ADA1 (usually mentioned as ADA) has a more prominent role catalyzing the irreversible deamination of Ado to inosine. ADA1 is widely expressed in lymphoid and non-lymphoid tissues, including the thymus, spleen, and intestine, among others, and it is also involved with neurotransmission. ADA2 can be found in the serum, liver, and monocytes/macrophages [54]. This isozyme has a key role in the regulation of immune responses; besides, it can induce proliferation of T helper cells and macrophages and prompt the differentiation of monocytes into macrophages [61].

2.3. Purinergic receptors

Purinergic receptors for nucleotides and nucleosides are widely distributed in cells and can be divided into two main types: P1 and P2 (Fig. 1). Nucleotides such as ATP, ADP, UTP and UDP bind to P2 receptors while Ado binds to P1 receptors. P2 receptors can be further subdivided into the P2X and P2Y families. There are seven P2X receptor subtypes ($P2X_{1–7}$), which are ionotropic receptors connected to channels in the cellular membrane [62]. $P2X_7$, one of the most studied and well-known P2X receptors, has key immunomodulatory functions [13]. It is a trimeric ion channel responsive to ATP and largely expressed in immune cells; thus, it plays key roles in several inflammatory events. $P2X_7$ activation triggers downstream signaling events with the release of pro-inflammatory cytokines, such as IL-1β [62–64].

P2Y receptors are metabotropic G-protein-coupled receptors (GPCRs) for extracellular nucleotides, such as ATP and ADP [54]. The eight subtypes can be divided into two subgroups: a) $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, and $P2Y_{11}$; and b) $P2Y_{12–14}$ [61,65,66]. These receptors are found in almost every cell type and have key functions in several pathophysiological conditions, including the regulation of inflammatory processes [66,67]. For instance, $P2Y_{12}$ antagonism is clinically used in cardiovascular interventions because this receptor is involved with ADP-induced platelet aggregation [68]. Clopidogrel and prasugrel and the nucleoside analogue ticagrelor are pharmacological strategies used for inhibiting platelet aggregation because they block $P2Y_{12}$ [68]. Besides, P2Y receptors also present modulatory effects in the nervous system by regulating neuronal and microglial activities [66].

P1 receptors can be divided into four subtypes (A_1, A_{2A}, A_{2B}, and A_3); all of them are GPCRs and have Ado as an agonist. Ado modulates several physiological functions in the central nervous system (CNS), cardiovascular system, and immune system, among others [26,60]. The A_1 and A_{2A} subtype of P1 receptors are particularly important in the brain and more and more data have highlighted their involvement in psychiatric and neurological disorders, including Alzheimer's and Parkinson's disease, depression, and bipolar disorders, among others. A_1 inhibitory receptors have been traditionally implicated with neuroprotection, while A_{2A} excitatory receptors have been suggested to play a major role in neurotoxicity and neuroinflammation [69–72].

Ado and ATP signaling through P1 and P2 receptors, respectively, has implications and therapeutic potential in cardiovascular pathophysiology [25]. For example, the participation of Ado in the modulation of glucose metabolism in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) has been proposed. In the pancreas, this nucleoside may participate in the proliferation and regeneration of β cells and thus also influence insulin secretion and perhaps affect insulin responsiveness in distant tissues, such as muscle, the liver, and adipose tissue [73].

In the immune system, both P1 and P2 receptors are key mediators of immune responses. While ATP accumulates at sites of cell damage and inflammation and acts fundamentally as a pro-inflammatory molecule through its binding to $P2X_7$ and triggers the activation of the NLR family

pyrin domain containing 3 (NLRP3) inflammasome and cytokine release, such as IL-1β, Ado functions mostly as an anti-inflammatory mediator through its binding to the P1 cell-surface receptors, also largely expressed on immune cells [24,63,74].

3. The role of the purinergic system in DM

DM is characterized by high blood glucose levels, which occur due to the absence of insulin owing to the autoimmune destruction of pancreatic β cells (T1DM) or resistance to this hormone (T2DM). Thus, the hormonal abnormalities of DM lead to chronic hyperglycemia that alters several metabolic pathways, especially in the metabolism of carbohydrates, lipids, and proteins. The main symptoms of the diabetic state include polyuria, polydipsia, weight loss, polyphagia and blurred vision. In more severe cases, ketoacidosis can occur, which can lead to coma and even death if left unchecked [75].

Furthermore, various mechanisms are involved in the secretion and action of insulin in physiological conditions, including those regulated by the purinergic signaling pathway, through the action of its nucleotides and nucleosides [14]. The effects of nucleotides, mainly ATP, on insulin secretion, has been known for many years. The specific ATP responses on insulin signaling are controlled by binding to both P2X and P2Y receptor subtypes, which mediate the stimulation or inhibition of glucose-induced insulin release [14]. Stimulated secretion of this hormone is related to the release of ATP through pannexin channels. Once ATP or another agonist binds to its respective receptor such as $P2X_7$, $P2Y_1$, or $P2Y_6$, insulin is secreted from β cells [76–78]. By contrast, P2 × 3 and $P2Y_{13}$ activation inhibits insulin secretion [14]. Through ATP signaling, ATP-dependent K^+ channels open occasionally and stimulate insulin release. In turn, the insulin-containing granules also contain ATP, indicating that this ATP release may have a role in insulin signaling [15]. In addition, glucagon-like peptide-1 (GLP-1) induces a glucose-dependent insulin secretory effect via elevation of cAMP and activation of protein kinase A (PKA), inhibiting pancreatic KATP channels [79–81]. Thus, nucleotide-mediated alterations in KATP channels cause a depolarization by changes in the intracellular ATP, ADP and glucose levels [80,82].

Extracellular ADP inhibits insulin secretion and causes β cell apoptosis by activating the $P2Y_{13}$ [83]. This receptor is related to glucotoxicity because it participates in insulin receptor substrate 1 (IRS-1) phosphorylation and affects the survival of β cells and insulin secretion [84]. In a similar way, the A_1 receptor—at a low Ado concentration—has inhibitory effects on insulin secretion via G_i proteins. These findings highlight the effect of the purinergic system on the normal insulin signaling in the pancreas. This system may also participate in changes promoted by a lack of insulin [15].

Disturbances in ATP homeostasis have been demonstrated in pathological conditions as DM [85]. Indeed, at the beginning of the disease, specifically during the processes of cellular and tissue damage like pancreatic β cell destruction, ATP functions as a damage signal, also known as molecular pattern associated with damage (DAMP) [12]. In this context, the complex pathogenesis of DM triggers chronic inflammation, with impaired β cell function mediated by ATP signaling, leading to activation of the NLRP3 inflammasome, inducing macrophage activation [86]. Other changes promote a decrease in anti-inflammatory IL-10 production concomitant with increased proinflammatory cytokines secretion that establish the diabetic proinflammatory state [84,87,88]. Thus, alterations in nucleotide metabolism participate in the pancreatic function regulation that is associated with DM development.

Modifications in nucleotide hydrolysis and in the expression of purinoreceptors in tissues/cells of central and peripheral systems promoted by hyperglycemia have been the focus of many studies in the recent decades. Table 1 provides the main findings, which have highlighted the important role of purinergic signaling during the development and advancement of T1DM and T2DM, as well as its possible involvement in the emergence of diabetes-related comorbidities.

The pioneering studies involving purinergic system and diabetes began in the 1970s, when Mikhail and Awadallah (1977) observed that the ATP given before alloxan, a glucose analog, could prevent a marked rise in blood sugar. This finding suggests that this nucleotide seems to be essential for both insulin secretion as well as glucose utilization by various tissues [89]. Subsequent evidence has revealed that P2R agonists (ADPbS, 2-MeSATP) stimulate insulin secretory responses and the vasodilator effects in pancreas of experimental T1DM model [90–92] as well as an insulinoma cell line [93].

Consistent with the idea that purinergic receptors play roles in diabetes progression, Coutinho-Silva et al. [92] observed $P2X_7$ upregulation in NOD mouse pancreas after 12 weeks of diabetes development; this change contributed to proinflammatory process associated with hyperglycemia. Another study reported similar effects in peripheral blood mononuclear cells (PBMCs) from T2DM patients [101]. Other studies have demonstrated that $P2X_7$ mediates NLRP3 inflammasome activation and establishes the proinflammatory responses [86,115,117].

Persistent inflammation in the diabetic state also is associated with the role of the $P2X_7$R-initiated signaling cascades in the activation of the transcription factors. For example, Ca^{2+} influxes induced by $P2X_7$R pore are associated with the nuclear translocation of both nuclear factor of activated T-cells (NFAT) and nuclear factor kappa B (NF-κB) [119]. In contrast, NF-kB pathway stimulates the production of inflammatory cytokines, linked to the development of insulin resistance [120,121], and anti-diabetic agent and AMP-activated protein kinase (AMPK) agonist, metformin, suppresses the inflammatory responses by downregulating phosphorylation of signal transducer and activator of transcription 3 (STAT3) in human liver cells [122].

Furthermore, Lunkes et al. 2003 [89], found that NTPDase (CD39) and 5′-NT (5′-nucleotidase; CD73) activities were enhanced in the platelets from patients with T2DM, hypertension or T2DM + hypertension. Subsequently, these enhancements in the platelet activities of CD39 and CD73 were confirmed in an animal model of T1DM induced by alloxan [33]. In addition, Lunkes et al. 2008 [114], demonstrated that the hydrolysis of adenine nucleotides was augmented in human platelets in the presence of increasing glucose and frutose concentration *in vitro* [114]. Taking together, these findings represent important contributions to elucidate the physiopathology of diabetes (hyperglycemia) related with the enzymes of the purinergic, mainly CD39 and CD73. It was considered as a compensatory mechanism in the platelet microenvironment trying to enhance the hydrolysis of ADP and the production of adenosine.

Among the ATP-degrading enzymes in pancreatic tissue, the most important role is attributed to the activity of NTPDase3, because high levels of its messenger RNA (mRNA) have been detected in human and mouse pancreatic islets, as well as in MIN6 cells (a mouse insulinoma cell line) [123]. In addition, CD39 expression reportedly influences susceptibility to diabetes induced by low doses of STZ: CD39 knockout mice develop diabetes more quickly than wild type mice [124]. By contrast, mice that overexpress CD39 do not develop the disease [124]. Moreover, it has been described that ectonucleotidases expression is regulated by several transcription factors, including STAT3 [125], which is involved in the development of skeletal muscle insulin resistance in T2DM patients [126], as well as the activation of STAT3 mutation causes neonatal DM associated with beta-cell autoimmunity through premature induction of pancreatic differentiation [127–129].

High glucose levels, also increased the expression of another nuclear factor of NFAT contributing to the progression of DM. NFAT promotes diabetic vascular complications, insulin resistance and induces inflammation at the onset stage of diabetes [130]. Indeed, hyperglycemia activates NFAT in native vascular smooth muscle by the releasing of extracellular nucleotides (i.e., UTP, UDP), which leads to an increase in intracellular Ca^{2+} levels by P2YR [131,132].

In addition, there are changes in adenosinergic pathway during diabetes. Diabetic patients present elevated ADA levels [109], and

Table 1
Main findings associated with DM and purinergic signaling in the last decades in chronological order.

Year	Subjects	Induction	Tissue / cell	Diabetes model	Outcomes	References
1977	Sprague Dawley adult female rats	Alloxan (150 mg/kg; i.p.)	Blood and liver	T1DM	ATP administration before alloxan prevented high blood glucose levels, ↓ fat and ↑ glycogen content in the liver	[89]
1989	Wistar adult male rats	STZ (single dose – 66 mg/kg)	Pancreas	T1DM	STZ suppresses the stimulatory effect of adenosine on α-cells and reduces its vasodilator properties	[90]
1992	Wistar adult male rats	STZ (single dose – 66 mg/kg)	Pancreas	T1DM	P2YR agonist (ADPβS) stimulates of insulin and has vasodilator effects	[91]
1996	Zucker adult male diabetic fatty rats	–	Pancreas	T2DM	Preservation of insulin secretory responses to P2 purinoceptor agonists (ADPβS, B-Me-ATP)	[92]
2002	INS-1 cells	–	–	–	↓ [ATP] modulates insulin release by $P2Y_1R$ ↑ [ATP] inhibits insulin release	[93]
2004	Wistar adult male Rats	Alloxan (150 mg/kg; i.p.)	Platelets and synaptosomes from cerebral cortex	T1DM	↑ NTPDase and 5′-NT enzyme activities	[94]
2007	C57BL/6 adult male mice and knockout $A1R^{(-/-)}$ mice	Glucose (1 g/kg body weight; i.p.)	Pancreas	T2DM	A1R deficiency increased insulin and glucagon secretion	[95]
2007	Wistar adult male rats	STZ (single dose – 65 mg/kg)	Cerebrospinal fluid and hippocampal membranes	T2DM	↓ [ATP] in cerebrospinal fluid. ↓ Density of P2Rs in hippocampal membranes	[96]
2007	Male and female adult NOD mice	–	Pancreas	T2DM	↑ Migration of $P2X_7^+$ cells from the periphery to the center of the islets	[97]
2007	Wistar adult male rats	Alloxan (150 mg/kg; i.p.)	Platelets	T2DM	↑ NTPDase and 5′-NT activities	[98]
2009	Wistar adult male rats	STZ (single dose – 55 mg/kg)	Platelets	T1DM	↑ NTPDase, 5′-NT, E-NPP and ADA activities	[33]
2009	Male and female adult patients (60.4 ± 8.5 years)*	–	Platelets	T2DM	↑ [ATP] and ↓ Mitochondrial membrane potential	[99]
2010	Male and female adult patients (56.8 ± 2.1 years)	–	Platelets	T2DM	↑ ADA and 5′NT activities	[100]
2010	MIN6c4 cell line	–	Cells	–	↑ expression of $P2Y_1R$ and $P2Y_{13}R$	[83]
2011	Male and female adult patients (45.6 ± 10.4 years)*	–	PBMC cells	T2DM	↑ $P2X_7R$ expression ↑ % of $CD39^+$ cells	[101]
2013	C57 BL/6 adult male mice and mouse Beta-TC6 cells	–	–	–	Adenosine receptor agonists (Cl-IB-MECA, CPA, CGS2168, NECA) ↑ insulin secretion	[102]
2013	Female adult NOD-mice	–	Pancreatic islets	T1DM	↓ A_1R expression	[103]
2014	Female and male adolescents patients (mean age 14.9 years)*	–	Treg cells	T1DM	Lower CD39 expression	[104]
2015	Wistar adult male rats	STZ (single dose – 55 mg/kg)	Platelets	T1DM	↑ NTPDase, 5′-NT, E-NPP and ADA activities	[36]
2015	Female and male adult patients (mean age 48 years)*	–	Treg cells	T2DM	↓ % of $CD39^+$ cells	[105]
2016	Wistar adult male rats	STZ (single dose – 70 mg/kg)	Synaptosomes from cerebral cortex	T1DM	↓ NTPDase activity ↑ ADA activity. Impairment of memory	[106]
2016	Female and male adult zebrafish (Danio rerio)	111 mM glucose solution in 5 L	Brain membranes	Hyperglycemia model	↓ Nucleotide hydrolysis ↑ ADA activity ↓ Gene expressions of adenosine and adenosine receptors	[107]
2016	Wistar adult male rats	STZ (single dose – 60 mg/kg)	Platelets and synaptosomes from cerebral cortex	T1DM	↑ADP and AMP hydrolysis in platelets ↑ platelet aggregation ↑ AMP hydrolysis in synaptosomes	[34]
2016	Wistar adult male rats	High-fat diet + STZ 35 mg/kg	Platelets	T2DM	↑ NTPDase, 5′-NT and ADA activities	[108]
2016	Female and male patients (mean age 58.5 years)	–	Serum	T2DM	↑ ADA levels	[109]
2016	Adult male mice	STZ (multiple low-dose – 50 mg/kg)	Hearts	T1DM	↑ A2AR expression in coronary arteries	[110]
2016	Male adult P2 × $7^{(-/-)}$ mice	STZ (multiple low-dose – 45 mg/kg)	Pancreas	T1DM	$P2X_7$ Knockout mice are resistant to TD1 induction ↓ Proinflammatory mediators	[111]
2017	Female and male adult patients (57 ± 6.3 years)	–	Platelets	T2DM	↑ $P2Y_{12}R$ activation	[112]
2017	Wistar adult male rats	STZ (single dose – 60 mg/kg)	Serum and platelets	T1DM	↑ NTPDase, 5′-NT and ADA activities	[113]
2018	Wistar adult male rats	STZ (single dose – 65 mg/kg)	Platelets, lymphocytes	T1DM	↑ NTPDase and ↓ 5′- NT in platelets ↑ NTPDase and ADA in lymphocytes	[37]
2018	Wistar adult male rats	STZ (single dose – 55 mg/kg)	Synaptosomes and total cerebral cortex	T1DM	↓ NTPDase activity and A_1R density ↑ $A_{2A}R$ and $P2X_7R$ density	[35]
2018		–	CD8+ effector T cells	T1DM	Up regulation of $P2X_7R$	[114]

(*continued on next page*)

Table 1 (*continued*)

Year	Subjects	Induction	Tissue / cell	Diabetes model	Outcomes	References
	Female and male patients newly diagnosed (10.2 ± 3.2 years) and long-standing T1DM (42 ± 12.3 years)					
2018	Male adult Db/db mice		Hippocampus	T2DM	NLRP3 inflammasome inhibition ameliorates diabetic encephalopathy	[115]
2019	Adult male ICR mice	STZ (single dose – 200 mg/kg)	Nitric oxide synthase neurons (NOS neurons)	T1DM	Up regulation of $P2X_7R$	[116]
2019	Wistar adult male rats	High-fat diet/ low-dose STZ – 30 mg/kg	Hippocampus	T2DM	NLRP3 inflammasome inhibition improves diabetes-mediated cognitive impairment	[117]
2019	MIN6 insulinoma cells	–	–	–	A_3R agonist, Cl-IBMECA, potentiated glucose-induced insulin secretion	[118]

* Hypoglycemiant therapy (insulin for T1DM, metformin/glibenclamide for T2DM).

oscillations in this enzyme level trigger significant changes that are mainly related to the activation/inhibition of Ado receptors. Indeed, Yip and colleagues [98] showed that a reduced A_1 receptor expression in pancreatic islets may contribute to the T1DM pathology in NOD-mice, and the activation of A_1 and A_{2A} receptors augmented insulin secretion, while the A_3 receptor is involved in the survival of mouse beta-TC6 cells [102].

Regarding Ado-mediated insulin secretion, the inhibition of the release of this hormone is attributed to the activation of the adenosinergic system [14,133]. Administration of A_1 receptor agonists is sufficient to stabilize glucose levels and increase sensitivity to insulin in tissues [134], while diminished A_1 receptor expression in pancreatic islets may contribute to the T1DM pathology [103]. Thus, the regulatory role of A_1 receptor activation by low concentrations of Ado could reduce insulin release from pancreatic β cells islets and favor the pre-diabetic condition [134]. Moreover, Ado signaling via the A_{2A} receptor is related to β cell proliferation, regeneration, and survival [73]. Additional A_{2A} and A_{2B} receptor activation protects islet grafts from T cell–mediated injury [124]. The A_3 receptor agonist, Cl-IBMECA, potentiates glucose-induced insulin secretion from MIN6 insulinoma cells possibly through transient Ca^{2+} entry [118]. Finally, an elevated Ado concentrations in endothelial cells due to adenosine kinase deficiency ameliorates diet-induced insulin resistance and metabolic disorders [135].

Thus, changes in the mechanisms of action of adenine nucleot(s)ides joint activation of P1 and P2 receptors leads to balanced regulation of blood glucose (Fig. 2) in the purinergic signaling pathway. These changes likely regulate vascular, immune, and nervous system complications that are associated with DM [12,25,85].

3.1. Involvement of purinergic signaling during DM: alterations related to blood vessels and the cardiovascular system

DM is associated with long-term damage to blood vessels, which

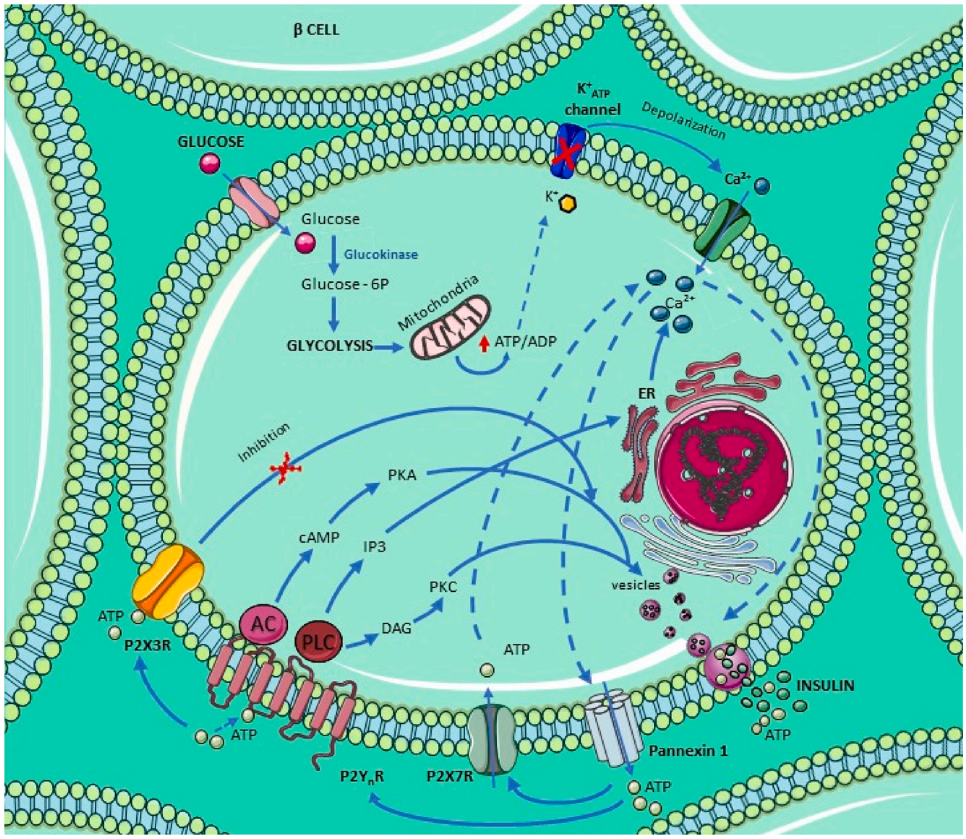

Fig. 2. ATP signaling in the purinergic system on insulin release.
The purinergic system and its role in the release of insulin from pancreatic β cells is influenced by the signaling of the ATP molecule. Glucose is transported into the β cell via its GLUT-2 transporter to be metabolized. The ATP generated from pyruvate catabolism and other biomolecules is exported from the mitochondria to the cytosolic compartment. ATP promotes the closure of ATP-sensitive K + channels in the plasma membrane, resulting in cell depolarization, calcium influx (Ca^{2+}) and consequent insulin release. In addition, stimulation of glucose-induced insulin secretion is also related to ATP release via pannexin 1 channels. Since ATP binds to purinergic receptors such as $P2X_7R$ (stimulating increased levels of intracellular Ca^{2+}), or $P2Y_1R$ and $P2Y_6R$ (either by activating second messengers such as cyclic adenosine 5′-monophosphate (cAMP), diacylglycerol (DAG) or by stimulating Ca^{2+} secretion by the endoplasmic reticulum (ER) and consequent intracellular increase), this nucleotide leads to secretion of insulin-containing vesicles by β cells. In contrast, the activation of $P2X_3R$ leads to inhibition of the secretion of this hormone. Source: Authors artwork.

triggers impairments in vascular smooth muscle and endothelial cells functions, related to dysregulation in the cardiovascular system [14,136]. Evidence provides that the distribution of purinergic receptors is altered during DM, mainly related to endothelial and smooth muscle cells, which can lead to crucial changes in vascular reactivity and vascular smooth muscle function [85,137]. Thus, hyperglycemia induces a paracrine and/or autocrine release of nucleotides that acts to bind purinergic receptors can modulate the vascular function [85].

Endothelial and vascular smooth muscle dysfunctions represent an early manifestation in vascular complications linked to diabetes. Recent studies point that the endothelial dysfunction in aortas of T2DM animals was attributable to activation of A_1R, $P2X_7R$, and $P2Y_6R$ [136]. Indeed, the $P2Y_6R$ modulating Ca^{2+} signaling and activation of the transcription factor NFAT during chronic elevations in extracellular glucose levels [131], NFAT is associated with vascular development during embryogenesis and causes enhanced vascular excitability [138,139]. Combined events increased NFAT nuclear accumulation and transcriptional activity, as a $P2Y_6R$, in order to induce the vascular dysfunctions observed in DM. Hyperglycemia also induces UTP release in smooth muscle cells, resulting in increases in the pro-atherogenic NFAT by $P2Y_2R$ and $P2Y_6R$ [131]. Thus, high extracellular glucose-induces release of ATP and/or UTP and reduces adenosine transport in endothelial cells [140].

Acute hyperglycemia also alters vascular smooth muscle excitability in the human and murine tissue, in which the $P2Y_{11}R$ or a $P2Y_{11}$-like receptor, respectively, plays a key upstream component in the signaling cascade regulating vascular reactivity in response to high glucose levels [141]. Similarly, in the STZ-induced T1DM model, $P2Y_1R$-mediated vasodilatation is impaired in superior mesenteric arteries [142].

Furthermore, the main vascular damage is related to high glucose levels, which increase the production of reactive oxygen species, leading to changes at the cellular level [143]. These changes often involve inflammatory processes in which purinergic signaling mediates the release of inflammatory cytokines [144]. Indeed, a reduction in the vasodilator effect of the purinergic system has been reported in patients with T2DM. However, it remains to be clarified to what extent the vasodilator capacity of nucleotides and nucleosides is compromised in DM [136].

ATP acts by regulating vascular tone through a double control pathway, being released during vasoconstrictive activity of the sympathetic nerve and during vessel relaxation due to its release from endothelial cells [25]. Besides, in vascular musculature, ATP can act as a vasoconstrictor or vasodilator via P2 receptors [145]. Similar to other extracellular nucleotides, uridine adenosine tetraphosphate (Up4A), an endothelium-derived vasoactive agent, is proposed to play a role in cardiovascular disorders and induces aortic contraction by binding to purinergic receptors [146]. Recent evidence has shown that the responsiveness to Up4A was altered in aortas of type 2 diabetic rats, associated with vascular complications in DM [147]. Additionally, an increased Up4A-mediated vasodilator influence via $P2Y_1R$ was observed in swine with metabolic derangement (DM and dyslipidemia) [148]. And Up4A induces aortic contraction, which partially requires the activation of $P2X_1R$ through an endothelium-dependent mechanism [149].

Mahdi et al. [136] suggested that endothelial dysfunction in the diabetic state occurs due to changes in the sensitivity of purinergic receptors. Thus, activation of P2Y receptors usually results in vasodilation due to the release of nitric oxide (NO) and prostacyclin. $P2X_7$ plays a crucial role in regulating vascular function in diabetes: In diabetic rats, renal vascular reactivity increased ATP release; ATP then bound to $P2X_7$ and led to its overexpression [150].

Platelet hyperaggregation and hypercoagulation are also associated with more macrovascular complications in a diabetic state [34,151]. Altered platelet morphology and function have been linked to hyperglycemia [152]. Thus, activation and recruitment of platelets to a damage site, due to vasodilation, are some of the effects mediated by ADP when it binds to specific purinergic receptors; ADP exerts its platelet aggregation effect mainly by binding to $P2Y_{12}$ [153]. Hu et al. [112] demonstrated that $P2Y_{12}$ upregulation contributes to platelet hyperactivity, facilitating a prothrombotic condition associated with T2DM patients. Likewise, the platelets of those affected by this disease have a high ATP content [99]. Besides, the main contribution of $P2Y_1$ is to change the platelets' shape, although this receptor also contributes to platelet aggregation [25].

Furthermore, the cardioprotective properties of Ado occur by activation of plasma membrane receptors at the vascular endothelium, an action that compensates for the platelet aggregation observed in DM. Among the Ado receptors, the A_{2A} receptor is relevant because it decreases platelet adhesion and activation by antagonizing ADP-mediated effects via $P2Y_{12}$ [154]. Indeed, A_{2A} receptor upregulation enhances coronary flow in diabetic hearts [110]. On the other hand, A_1 receptor activation results in lower cAMP levels and increased thromboxane release, inducing platelet activation and aggregation, which contribute to thrombus formation [155].

Moreover, several studies have reported alterations in ATP, ADP, and AMP hydrolysis in platelets during DM, including elevated CD39, E-NPP, CD73, and ADA activities in platelets from T1DM and T2DM in rats [36,37,98,100,108]. The increase in ATP hydrolysis by CD39 depletes the levels of ADP, an agonist of platelet aggregation [37]. Consistently, Stefanello and colleagues [34] showed that high glucose concentrations increase CD39 and CD73 activities *in vitro* in platelets, and there is elevated platelet aggregation in STZ-induced diabetic rats [34].

3.2. Involvement of purinergic signaling during DM: microvascular complication

Diabetic nephropathy is among the most prominent microvascular complications of DM. Diabetic nephropathy is a serious diabetic complication characterized by thickening of the basal and glomerular renal membranes, accumulation of extracellular matrix proteins, and progressive mesangial hypertrophy [156]. In DM, glomerular hyperfiltration may be due to changes in vasoconstriction due to a decrease in NO levels, which are influenced by Ado levels and their binding to the A_{2B} receptors [14]. $A_{2B}R$ mediates the transforming growth factor-beta 1 (TGF-β1) release from glomeruli of diabetic rats [157], and induces the vascular endothelial growth factor (VEGF) in the glomerular podocytes of diabetic rats [158], these events favoring the pathogenic state support the progression of glomerulopathy.

The second abnormality related to chronic DM is diabetic retinopathy. Abnormalities in the eye capillaries are observed during the early stage of the disease. Thus, researchers have proposed that high glucose levels alter the purinergic signaling system in the retina [14]. Vindeirinho et al. [159] reported that in conditions of hyperglycemia the retina of rats is affected; this phenomenon could be related to changes in the Ado signaling mechanism, including an increase in A_1 and A_2 receptors expression accompanied by a decrease in ADA expression.

3.3. Involvement of purinergic signaling during DM: alterations related to the CNS

Although the major changes from chronic hyperglycemia occurs on peripheral cells, DM is associated with dysfunction in neurotransmission systems, including the purinergic system and memory impairment [96]. Capiotti and colleagues [107] revealed a decrease in ATP, ADP, and AMP hydrolysis and an increase in ADA activities from encephalic membranes of hyperglycemic zebrafish, as well as a decrease in ADA and Ado receptor gene expression. A previous study reported similar alterations in ATP signaling and Ado receptor density in the cerebral cortex of diabetic rats, with A_1 receptor downregulation and A_{2A} receptor and $P2X_7$ upregulation in the cerebral cortex [35]. Reduced A_1 receptor signaling is associated with impaired glucose tolerance and insulin resistance [160]. Furthermore, the A_{2A} receptor triggers noxious effects, such as cognitive decline and memory loss [50,161]. $P2X_7$ upregulation induces proinflammatory processes in high-glucose-exposure conditions

[13].

Consistent with the above-mentioned results, the impairment of memory and the anxiogenic-like behavior, as well as a decrease in the NTPDase and increase in the ADA activities in the CNS from the cerebral cortex of diabetic rats, are correlated with insulin deficits [106]. Indeed, high levels of extracellular ATP can lead to deleterious effects on the brain: ATP activates $P2X_7$ and promotes the influx of intracellular Ca^{2+}, which leads to the activation of apoptotic pathways, production of reactive oxygen species, excitotoxicity, and neurodegeneration [162,163].

Diabetes-induced damage of NO-producing neurons is mediated by $P2X_7$ in diabetic mice via pannexin-1 [116]. In addition, inhibition of NLRP3 inflammasome activation ameliorates diabetic encephalopathy in db/db mice (a T2DM model), similar to the cognitive impairment and vasoneuronal remodeling that occurs after ischemia in diabetic Wistar rats. Thus, inhibitors of the NLRP3 inflammasome and/or purinergic molecules involved in proinflammatory cascade represent a potential therapeutic strategy to slow the cognitive decline in diabetic individuals and in patients following stroke and neuroinflammation induced by hyperglycemia [115,117].

3.4. Crosstalk between purinergic and immune systems in DM context

Changes in β cell metabolism commonly cause toxicity and result in cell death by apoptosis or necrosis [164]. In the early stage of DM, there is an increase in pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), IL-1, and IL-6 [165]. A chronic inflammatory state is established as the disease evolves, with the persistence of proinflammatory cytokines above normal levels, a process that may be associated with atherosclerosis in diabetic individuals [166]. Furthermore, immune cell infiltration triggers a release of proinflammatory cytokines, macrophages, and T cells, all of which contribute to insulin resistance [88].

Studies have implicated proinflammatory cytokine release, alterations in leukocyte populations, and apoptosis stimulation in DM [167–169]. In corroboration with these dysfunctions, lower CD39 expression on $CD4^+$ regulatory T cells (Treg) is associated with metabolic factors in T1DM and T2DM patients [76,104,105,170]. However, Pereira and colleagues [38] showed alterations in purinergic signaling in lymphocytes of diabetic rats and point to an increase in the CD39 and ADA. The increase in CD39 can reflect the high levels of ATP, which can activate T cells by engaging $P2X_7$ [24], while an increase in the ADA activity reduces anti-inflammatory Ado levels [37].

In addition, a recent study revealed that $P2X_7R$ knockout prevented STZ-induced T1DM in mice and did not increase the levels of proinflammatory mediators (IL-1β, interferon-γ and NO), with reduced immune cell infiltration in the pancreatic lymph nodes [171]. However, NOD mice exhibited increased NLRP3 inflammasome and IL-1β gene expression in pancreatic lymph nodes, conditions that predisposes to T1DM in murine model [11]. $P2X_7$ is upregulated on $CD8^+$ effector T cells in patients with T1DM, and $P2X_7$ blockade reduces the $CD8^+$ T cell–mediated autoimmune response *in vitro* and delays diabetes onset in NOD mice [114]. There are more $P2X_7^+$ cells in PBMCs isolated from T2DM patients [101], results that emphasize the pro-inflammatory process triggered by purinergic markers.

3.5. Involvement of purinergic signaling during DM and hypertension

Hypertension is a major risk factor for cardiovascular disease and, particularly, in DM patients. Around 40 %–60 % of diabetes patients exhibit high blood pressure (BP) [172]. As a result of its role as a major risk factor, there has been substantial research, both basic and clinical, in the pathogenesis of hypertension, specifically including DM as well as the clinical management and treatment of hypertension in DM. The coexistence of hypertension and DM is associated with a sixfold increase in the risk of cardiovascular events compared with healthy subjects [173].

The global epidemic of hypertension is largely uncontrolled, and throughout the world, hypertension remains the leading cause of noncommunicable disease deaths. It is projected to rise from 918 million adults in 2000 to 1.56 billion in 2025 [173]. Hypertension is defined as systolic blood pressure (SBP) $\geq$ 140 mmHg, or diastolic blood pressure (DBP) $\geq$ 90 mmHg, or antihypertensive adhesion treatment [6]. Briefly, BP is controlled by the relationship between circulatory fluid volume and peripheral vascular resistance [174].

The period from the initial impairment of glucose tolerance to diabetes onset is characterized by both hyperglycemia and hyperinsulinemia with insulin resistance. During this period, the main metabolism that underlies elevated BP is the promotion of sodium reabsorption due to higher insulin levels and excessive body fluid due to hyperglycemia-induced osmolar adjustment that can progress to hypertension [175]. Although high BP is largely asymptomatic, especially in the early stages, the relationship between hypertension and diabetes complications can be classified as acute and chronic [176]. In the early stage of diabetes, both hyperglycemia and hyperinsulinemia can promote vascular remodeling. The gradual progression of vascular remodeling leads to increased peripheral arterial resistance and eventually contributes to hypertension.

Hypertension influences the development of diabetic nephropathy, which pathologically comprises the following: thickening of the glomerulus and renal tubule basement membrane, mesangial and interstitial proliferation, endothelium denaturation, and interstitial changes involving exudative lesions in small vessels. There are also proinflammatory reactions such as T lymphocyte permeation and small vessel hyperplasia [177]. These changes are caused by hyperglycemia-induced glomerular circulation and renin–angiotensin system stimulation [178], glycation [179], and oxidative stress [180]. There are also intracellular metabolic abnormalities such as polyol and protein kinase activation, microinflammation, cytokine production, and extracellular matrix production or resolution [181].

The stages that involve advanced vascular remodeling lead to pancreatic β cell loss and attenuation of insulin secretion, with a corresponding reduction in sodium reabsorption by insulin [182]. At this time, the main mechanism that causes BP elevation is increased peripheral arterial resistance because the increase in body fluid is stable—with only osmolar adjustments due to hyperglycemia. Acute complications include diabetic ketoacidosis, nonketotic hyperosmolar coma, and hypoglycemia. Chronic complications include microvascular injuries such as neuropathy, retinopathy, and nephropathy. By contrast, macrovascular complications contribute to the pathogenesis of cardiovascular disease, such as coronary, cerebrovascular, and peripheral arterial diseases [183].

Several pathogenic mechanisms have been proposed to explain the association between DM and hypertension; they are thought to be mediated through the adrenergic system [183]. Such mechanisms include incretin-mediated control of the renin–angiotensin–aldosterone system. Alterations in the Ca^{2+}/calmodulin system elevate intracellular Ca^{2+} levels, which inhibit transcription of the insulin gene in pancreatic β cells [184]. These changes lead to the development of diabetic nephropathy, extracellular fluid expansion, and increased arteriole stiffness.

Although there are myriad mechanisms that are relevant in the coexistence of DM and hypertension, purinergic signaling has emerged as a complex system that contributes significantly to hypertension and DM. According to Burnstock [25], there seems to be different ways that purinergic signaling contributes to the development of hypertension. In the first pathway, ATP released as a cotransmitter with noradrenaline from sympathetic nerves acts on $P2X_1R$ to constrict vascular smooth muscle. Using human samples, *in vitro* strategies, and a rat model, Helenius et al. [185] demonstrated that CD39 suppression is linked to the pathogenesis of hypertension. Furthermore, they stated that the accumulation of extracellular ATP and ADP is strictly linked to vascular

dysfunction and remodeling in hypertension and can modulate the disease course at multiple levels. Increased in CD39 nucleotidase in vascular murine adventitial cells also suggests that this enzyme plays a role in hydrolyzing the ATP released from sympathetic nerves and, thus, can help to control vascular tone and hypertension development [186]. Augmented CD39 and CD73 activities have been observed in animal hypertension models, in human studies, and in platelets and lymphocytes [40,187,188]. These specific platelet and lymphocyte responses can be understood as a mechanism to ameliorate hypertension through the elevation of Ado levels, by combined actions of CD39 and CD73 [40].

In the second pathway, ATP is released from endothelial cells during shear stress produced in response to changes in blood flow; the released ATP then acts on P2 receptors, particularly $P2X_1$, $P2X_4$, $P2X_7$, $P2Y_1$, $P2Y_2$, $P2Y_6$ and $P2Y_{12}$ receptors subtypes on endothelial cells, to release NO, resulting in vasodilation and a decrease in BP [25]. ATP and UTP stimulate vascular smooth muscle cell proliferation in the spontaneously hypertensive rat (SHR) via $P2Y_2R$ and/or $P2Y_6R$ [189], and $P2Y_2R$ activation is linked to mechanisms that contribute to decreases BP [190]. In contrast, impaired UTP-induced rat carotid arterial relaxation endothelium-dependent in SHR arteries through impaired $P2Y_2R$, in the contribution of other receptors, as $P2Y_4R$ and $P2Y_6R$. Thus, occurs the UTP-mediated vasomotor response in hypertension-associated vascular complications [191]. In addition, mice with endothelium-specific $P2Y_2R$ deficiency lacked flow-induced vasodilation and developed hypertension accompanied by reduced endothelial nitric oxide synthase (eNOS) activation [192]. Another factor that contributes to the occurrence of hypertension is $P2Y_6R$ dimerization with the angiotensin II type 1 receptor, thus angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can be widely used in the treatment of hypertension [193].

P2R also implies a potential role in vascular activity via Up4A. It has been related that the plasma level of Up4A is elevated in hypertensive patients. Indeed, Up4A-mediated aortic contraction through $P2X_1R$ and the vasoactive effect of Up4A was impaired in aortas isolated from Ang II-infused hypertensive mice. Thus, the vascular $P2X_1R$ activity, rather than plasma Up4A level, may determine the role of Up4A in hypertension, contributing to high blood pressure [149,194,195]. In addition, the pressure overload-induced coronary vascular remodeling results in attenuation of the vasodilator effect of Up4A, which is accompanied by increased expression of $P2Y_{12}R$ [196]. Therefore, Up4A-P2R signalling implies a crucial role in cardiovascular complications associated with hypertension.

In relation to $P2X_7R$, this receptor plays a key role in the development of hypertension via increased inflammation [197]. Antagonism of $P2X_7R$ reduces BP in Ang-II–treated rats [198]. Interestingly, genetic alterations in a region of the $P2X_7R$ and $P2X_4R$ genes affect the BP in humans, and drugs that modulate P2XR signalling in vascular endothelium provide the clinical antihypertensive agents [199]. Thus, ATP/UTP plays an important role in hypertension, and purinergic receptors are linked to platelet activation and aggregation, vasoconstriction, and low-grade inflammatory status are all related to hypertension.

Similarly to DM, in hypertensive patients and in animal models, occurs an increase of the prototypic transcription factor, NF-κB [200], which leads to increased tissue and/or circulating levels of proinflammatory mediators. In addition, autocrine purinergic signaling is required for the full expression of the NFAT gene under hyperosmotic conditions, once that NaCl-induced NFAT gene expression dependent in part on the activity of NF-κB [201]. Activators of Gq-coupled receptors (i.e. Ang II, catecholamines, UTP), increase the plasma glucose levels and intravascular pressure by activating of NFAT [202]. In contrast, the inhibition of STAT3 prevented the Ang II–induced vascular dysfunction of the murine carotid artery and reduced the hypertension development-induced to Ang II [203,204].

Changes in ADA expression and activity are also related to hypertension development and maintenance. Indeed, ADA activity and platelet aggregation could serve as peripheral markers for the development of therapy for the maintenance of homeostasis and inflammatory processes in hypertension and hypertension-associated pathologies [205]. A genetic study with hypertensive patients showed that a common polymorphism (C34 T) of the ADA gene (isoform 1) is strongly correlated with hypertension [206].

ADA activity is also increased in platelets and lymphocytes in an animal model of hypertension induced by L-NG-Nitroarginine Methyl Ester (L-NAME) administration [187,188]. Moreover, Tofovic et al. [207] suggested that ADA inhibition may provide beneficial effects in old hypertensive animals, and an inhibitor of this enzyme could be designed and used to offer cardiovascular protection in hypertension. Franco and colleagues [208] analyzed the activity of nucleotidases and ADA in cytosolic and membrane fractions of renal tissue from an Ang-II model of hypertension. They observed a decrease in the membrane ADA activity and expression in AngII-treated rats. These results suggest that elevated renal tissue and interstitial Ado levels contribute to the renal vasoconstriction observed in the AngII-induced hypertension. This can be mediated by either a decrease in the activity and expression of ADA, or increased production of Ado, or an imbalance in Ado receptors [25].

In addition, all adenosine receptors are expressed in vascular smooth muscle and endothelial cells, and play a crucial role in control of vascular tone and cell proliferation in several diseases associated to cardiovascular risk, as diabetes and hypertension [209]. In $A_{2A}R$ knockout mice was observed an increased in endothelial cells proliferation, as well as in smooth muscle hypertrophy. Perhaps, Ado acts by $A_{2A}R$ triggers an important regulatory mechanism to protect against development of hypertension [210]. Similarly, endothelial cell proliferation and angiogenesis also is mediated by $A_{2B}R$, which exerts some mitogenic effects mediated via modulation of the VEGF signaling [211].

In contrast, elevated CD73-mediated high levels of renal Ado, that enhanced hypoxia-inducible factor-1α (HIF-1α) by the activation of $A_{2B}R$, resulting in elevated renal endothelin-1 production and leading to the development of hypertension [212]. In parallel, low ADA expression and activity are a potential strategy to increase antithrombotic and anti-inflammatory effects.

4. Therapeutic approaches related to purinergic signaling for DM and hypertension

4.1. Role of physical exercise and purinergic axis in DM

For a long time, physical exercise has been utilized to improve people's quality of life. Regular exercise can improve the immune system and, thus, it has become the target of studies for the prevention and treatment of numerous diseases, such as obesity, Parkinson's and Alzheimer's disease, multiple sclerosis, cancer, depression, diabetes, and hypertension, among others. Part of the benefits associated with exercise are its anti-inflammatory and antioxidant effects that during the chronic phase. Hence, it can be a very powerful preventive tool and an excellent adjunct in the treatment of these diseases [213]. Moreover, skeletal muscle is the primary site of whole-body glucose disposal and is plays a vital role in determining the overall insulin sensitivity and carbohydrate management. Physical exercise is important to stimulate muscle glucose transport and glycogen metabolism [214]; given this role, it is an excellent tool for DM patients, especially those with T2DM.

In T1DM, there is limited information about physical exercise because exercise does not increase insulin production and it is difficult to coordinate training, food intake, and insulin administration in T1DM patients. However, physical exercise is very important for the diabetic population. Reddy et al. [215] compared aerobic exercise and resistance training to see which protocol would bring the greatest benefits. The aerobic exercise group used a treadmill and spent 60 % of the time with controlled blood glucose; this control was not different from the control group, which spent 56 % of the time with controlled blood glucose. The group that performed the resistance training protocol-controlled blood

glucose for 70 % of the time, a significant difference compared with the aforementioned control group. One of the explanations for the greater benefit of resistance training is the fact that most of the glucose uptake generated by insulin occurs in the muscle [215].

Thus, working several muscles at high intensity increases the efficiency of insulin: The same amount of this hormone has better effects and reduces the need for insulin. Considering that strength training provided greater benefits than aerobic training, Farinha et al. [216] evaluated strength exercises and a high intensity interval protocol; they verified the chronic effect of these exercises. Strength exercise caused hypertrophy and increased strength while interval training improved cardiorespiratory fitness, oxidative capacity, and acidosis tolerance. Both protocols offered benefits in glucose homeostasis, oxidative stress, and inflammatory parameters in patients with T1DM [216].

T2DM patients have lower levels of strength and muscle flexibility and less aerobic capacity compared with healthy individuals of the same age and sex; therefore, aerobic and strength training is widely recommended. Strength training can improve or increase the action of insulin, control blood glucose levels, decrease the risk of cardiovascular disease, reduce mortality, prevent complications related to DM, and improve the quality of life of diabetics when practiced continuously [217]. Motiani et al. [217] compared two training protocols in prediabetic and T2DM individuals and found that, after a 2-week training period, both the moderate intensity continuous training protocol (MICT) and the sprint interval training (SIT) reduced liver fat content and inflammatory markers. In addition, MICT increased the uptake of glucose stimulated by insulin in the liver and reduced the uptake of free fatty acids in the same tissue [217].

The role of the purinergic system in exercise in diabetic individuals has received little attention. Osorio-Fuentealba and collaborators [218] used an electrical stimulation performed on the muscle to mimic exercise in a study involving both animals and cell culture. They found that stimulation transiently elevated extracellular ATP and caused GLUT4 receptor translocation to the cell surface in normal and insulin-resistant adult muscle fibers, similar to the reported effect of exercise [218]. Rodrigues and collaborators [219] explored the role of $P2X_7R$ in the kidneys of diabetic rats subjected to aerobic training on a treadmill. The authors found increased $P2X_7R$ expression in control animals. Exercise reduced this alteration and thereby might represent an adjunctive treatment to slow the progression of diabetic nephropathy [219]. Taghizaedh et al. [220] evaluated the expression of the $P2Y_{12}R$ in platelets of sedentary diabetic patients and, after 8 weeks of moderate intensity training on the treadmill, there was no significant change compared with the control diabetic group. In addition, there was also no change in platelet aggregation induced by ADP in the evaluated groups. It is suggested that a longer training period is necessary to generate significant results [220].

4.2. Role of physical exercise and purinergic axis in hypertension

Practicing physical exercises can prevent up to 19 % of cardiovascular diseases, such as hypertension. This percentage can increase for those who perform more hours of exercise, reaching up to 33 % for those who exercise 6 h per week. In addition to prevention, exercise can also lower resting BP [221]. The exercise-induced benefits toward hypertension are related to oxidative stress modulation: Physical exercise has antioxidant characteristics, and hypertension is linked to oxidative stress. Aerobic exercise, for example, shows benefits such as: improves vasorelaxation by increasing NO release, reduces SBP and DBP, and increases antioxidant levels. In a hypertensive rat model, aerobic exercise reduced BP; improved kidney NO levels; prevented oxidative damage; and improved antioxidant defenses in the kidney, serum, and plasma [222]. Combining aerobic and resistance training improves mean arterial BP and cardiovascular autonomic control and prevents cardiac and renal oxidative stress and inflammation in an experimental hypertension model [223]. In studies with isometric exercises, SBP decreased significantly after training and decreased oxygen-induced radicals induced by exercise. Tai Chi exercise stimulated endogenous antioxidant enzymes and reduced oxidative stress markers in addition to reducing SBP [224,225].

High intensity exercise, in turn, seems to have greater benefits for hypertensive patients. A study comparing aerobic exercise with high-intensity intermittent training (HIIT) showed that the latter resulted in a greater increase in aerobic fitness in less time and produced greater changes in arterial stiffness, endothelial function, insulin resistance, and mitochondrial biogenesis [226]. Another study comparing different protocols for intense exercise also suggested that HIIT has greater benefits, such as improved maximal oxygen uptake (VO_2max) compared with moderate intensity exercises [227]. Bahmanbeglou and colleagues [228] also confirmed that HIIT improves SBP and inflammatory markers in hypertensive patients, and also demonstrated that these results do not depend on the intensity and duration of HIIT.

Much recent research has involved physical exercise, hypertension, and the purinergic system. In the hypertensive population, exercise-induced modifications of the expression of many components improved cardiovascular parameters (e.g., BP, lipid metabolism, resting heart rate, thrombosis events, glucose intolerance, autonomic balance) as well as musculoskeletal, pulmonary, sleep quality, mood, immunity, and general fitness characteristics [229]. Purinergic system components might be one of the signaling mechanisms that underlies the exercise-related body improvements [40,187,213,230,231].

The balance between ATP and Ado concentrations, which are controlled by ectonucleotidases (CD39 and CD73), is crucial in exercise-dependent immune and platelet homeostasis. Extracellular ATP is a danger signal released by dying and damaged cells (which can occur during an exercise session) and it functions as an immunostimulatory signal that promotes inflammation. However, extracellular Ado acts as an immunoregulatory signal that modulates the function of several cellular components of the adaptive and innate immune response. CD39 and CD73 cooperate in the generation of extracellular Ado through ATP hydrolysis, thus tilting the balance toward immunosuppressive microenvironments. There is a duality between exercises effects. While acute intense exercise is associated with tissue damage, inflammation, and platelet aggregation, chronic exercise exerts anti-inflammatory and antiaggregant effects, promoting health [208,232]. All of these effects depend on purinergic signaling.

Related do the acute effects of physical exercise, our research group has shown that after 1 h of moderate swimming, there was a decrease in ectonucleotidase activities in rat lymphocytes [187] and an increase in ectonucleotidase activities in rat platelets [27]. These acute alterations may explain the role of chronic moderate swimming training in reduce platelet aggregation and SBP in a model of hypertension. In a recent study published by our research group [233], we tested three acute exercise protocols: 1) high intensity aerobic (HIAE), 2) low intensity aerobic (LIAE), and 3) LIAE + blood flow restriction (BFR) in elderly hypertensive woman. There was reduced ADA activity in lymphocytes after a 30-minute recovery following the HIAE and LIAE + BFR protocols compared with the other protocol and immediately after exercise. This ADA activity reduction positively correlates with the SBP reduction; this correlation suggests that more Ado is probably available after exercise to induce vasodilation and, thus, mediate the hypotensive exercise effects.

Related to the chronic effects of physical exercise in purinergic system components, Mortensen et al. [234] investigated aerobic training for 8 weeks in hypertensive and normotensive individuals. They aimed to examine whether functional sympatholytic and ATP signaling are impaired in the leg of hypertensive individuals and to determine the effect of aerobic training on these parameters. Training reduced BP in hypertensive individuals and hyperemia during exercise was similar to normotensive individuals in the trained state. There was no difference in the vasodilator response to the infused ATP or in the content of the muscle $P2Y_2R$ between the groups before and after training. However, the training reduced the vasodilatory response to ATP and increased the

skeletal muscle $P2Y_2R$ content in both groups. These results indicate that exercise training improves functional sympatholysis and reduces post-junctional α-adrenergic responsiveness in both normo- and hypertensive individuals [234].

Neurocirculatory responses to exercise are known to be exaggerated in hypertension and this increases cardiovascular risk. To better elucidate the mechanisms involved in this response, Greaney et al. [235] examined the contribution of P2 receptors to neurocirculatory responses to exercise in elderly people with moderately high SBP). Compared with normotensive adults (63 ± 2 years, 117 ± 2/70 ± 2 mmHg), adults with moderately high SBP (65 ± 1 years, 138 ± 5/79 ± 3 mmHg) demonstrated greater increases in muscle sympathetic nerve activity (MSNA) and BP during handgrip and static wrist, followed by post-exercise ischemia. Compared with the control group, local P2 receptor antagonism during PEI partially attenuated MSNA (39 ± 4 vs 34 ± 5 bursts/-minute; $P < 0.05$) in adults with moderately high SBP. These results indicate that pyridoxal-5-phosphate is an effective P2R antagonist in dorsal root ganglion neurons isolated from mice, which are of particular relevance to the pressure reflex of exercise [235].

We have studied the purinergic system and aerobic exercise in hypertension [187,231]. We submitted hypertensive Wistar rats (induced by L-NAME) to a 6-week swimming protocol and assessed the chronic effect of aerobic exercise and then evaluated the components of the purinergic system. The group treated with L-NAME presented elevated SBP and CD39 and ADA activities. Six weeks of swimming training prevented these changes and kept SBP and enzyme activities at the same levels as the control group. The exercise itself was associated with a decrease in CD39 expression in lymphocytes [187]. In another study, physical exercise reduced BP and prevented memory impairment induced by the L-NAME model of hypertension. Treatment with L-NAME elevated CD39, NTPDase3, and CD73 expression and activity in the cortex. $A_{2A}R$ expression increased in the hippocampus and cortex in the hypertension group and exercise prevented this overexpression [231].

A recent study evaluated the effect of 6 months of moderate resistance training, twice a week, in hypertensive elderly women. This protocol reduced BP, IL-6, C-reactive protein, and ATP levels as well as CD39 and ADA activities in the hypertensive group. Physical training was increased IL-10 levels in the hypertensive group. There was a positive correlation between BP, enzyme activities, and ATP and IL-6 levels; between CD39 and IL-6 levels; and between ATP levels and IL-6 levels. These findings demonstrated the relationship between purinergic signaling and inflammation in hypertension and suggests that resistance training serve as tool to reduce inflammation in hypertensive woman by modulating purinergic system [236].

There are still a limited number of studies that have explored the effect of physical exercise on hypertension and DM, and this number is even lower when exercise is tested when the body is already responding to these diseases. So far, it is known that the chronic effects of exercise can be an adjuvant in the treatment of hypertension and DM; these effects can be related to the purinergic system since both are associated with inflammatory and anti-inflammatory effects.

4.3. Natural compounds that modulate purinergic signaling during DM and hypertension

Several molecules that can modulate ectonucleotidases and ADA activities, as well as act as purinoceptor agonists or antagonists, are protective targets in different cells susceptible to the effects of diabetes. Indeed, flavonoids play a potential role in the modulation of the purinergic system, in both enzymatic activities and receptors expression [34–37,106,237]. In this way, the interaction of flavonoids with ATP/Ado receptors may possibly block noxious effects of metabolic disorders and thus ameliorate the diabetic condition and comorbidities. Hence, modulating the purinergic axis at different levels can prevent or protect the emergency of DM.

Polyphenolic compounds in red wine cause release of nucleotides from endothelial cells resulting in vasodilation, thereby decreasing BP [232]. In addition, a wide range of phenolic compounds modulate important components of the purinergic system during diabetes and hypertension. Resveratrol (3,5,4′-trihydroxystilbene), quercetin (3,3′,4′,5,7-pentahydroxyflavone), gallic and chlorogenic acid, Lingonberry, and ginger, among others, modulate the ectonucleotidase activities in several cells and tissues, as well as alter P2 and P1 receptor expression [33–35,37,106,188]. Given the importance of the purinergic system in diseases such as DM and hypertension, the interaction of phenolic compounds with ATP/Ado receptors may block the noxious effects of these disorders. Hence, modulating the purinergic axis could represent a therapeutic target to prevent the emergence of DM and hypertension.

Resveratrol is a natural and biologically active compound present in different plant species. Resveratrol has been described as an antioxidant, a cardioprotector, an antitumor and anti-inflammatory molecule, and a neuroprotector [238]. Furthermore, it has been associated with vasodilation and prevention of excessive platelet aggregation [33], and studies have shown that resveratrol decreases blood glucose levels in animals with experimental T1DM [237,239,240]. Resveratrol also reportedly attenuates autoimmune destruction of β cells by inhibiting the migration of inflammatory cells [241]. With regard to T2DM, a resveratrol-induced decrease in insulin resistance results from changes in skeletal muscle, the liver, and adipose tissue [238]. This mechanism of the action involves sirtuin 1 (SIRT1) activation in mammalian tissues [242]. In addition, diabetic rats that received red wine and grape juice showed an increase in CD39, E-NPP, and CD73 activities in platelets [237].

Quercetin is a flavonoid found in many vegetables, fruits, nuts, flowers, barks, broccoli, olive oil, bulbs and tubers, herbs, spices, tea, and wine. Quercetin is known for its anti-inflammatory, antihypertensive, vasodilator effects, anti-obesity, anti-hypercholesterolemic, and anti-atherosclerotic activities [243,244]. A study with quercetin supplementation (500 mg) in nonprofessional, healthy athletes who exercised regularly demonstrated a decrease in C-reactive protein [245]. In addition, quercetin inhibits platelet aggregation and reduces BP in hypertensive subjects [246]. In a hyperglycemic state promoted by STZ injection, quercetin (25 and 50 mg/kg doses) stimulated insulin secretion [247].

Other molecule studied by biological effects in the healthy human is chlorogenic acid (CGA, mainly 5-CQA). Structurally, chlorogenic acid is the ester formed between caffeic acid and the 3-hydroxyl of L-quinic acid [248]. CGA has a variety of biological proprieties described such as antioxidant, antiinflammatory, neuroprotective and hypoglycemic [34,249–252]. CGA treatment (80 mg/kg/d) promoted a significantly decreased in percentage of body fat, fasting plasma glucose and glycosylated hemoglobin (HbA1c) in the diabetic db/db mice [253]. In a randomized, double-blind, placebo-controlled clinical trial, patients with impaired glucose tolerance exposed to 400 mg CGA administered three times a day for 12 weeks showed a reduction in fasting blood glucose [254]. Moreover, Stefanello and co-authors [34] showed CGA as an anti-aggregant agent since CGA treatment reduced platelets aggregation when ADP was used as agonist as well as CGA showed a decrease in NTPDase activity in platelets of the diabetic group treated with 5 mg/kg chlorogenic acid [34]. This antiaggregant effect was related with activation by the A_{2A} receptor/adenylate cyclase/cAMP/PKA signalling pathway [255].

Along with chlorogenic acid, caffeic acid (a compound derived from caffeic acid in metabolism) has important effects on platelet aggregation [256,257]. Male rats treated with caffeic acid at doses of 10, 50 and 100 mg/kg decrease platelet activation when ADP and collagen were used as agonists. This effect highlights the role of these phenolic acids in hemostasis, especially when associated with pathologies that affect the correct functionality of platelets [258].

4.4. Clinical purinergic targets used in DM and hypertension

Nucleot(s)ides mediate the effects of vascular tone, inflammation and thrombosis by binding with specific receptors. Antithrombotic actions are attributed with $P2Y_1R$ antagonism as a complement to current $P2Y_{12}R$ antiplatelet strategies. Furthermore, the $P2X_1R$ is linked to vasoconstrictor mechanisms [259], while actions mediated by $P2Y_2R$ are involved with the regulation of angiogenesis [260]. In contrast, Ado plays antithrombotic effects by $A_{2A}R$, $A_{2B}R$ and A_3R [261,262]. Thus, the agonism/antagonism of P1 and P2 receptors represent a potential therapeutic target can be used in cardiovascular dysfunction involved in diabetes and hypertension complications.

In general, clopidogrel, a $P2Y_{12}R$ antagonist, is used clinically to inhibit platelets aggregation for thrombosis and stroke [163,263]. Similarly, others $P2Y_{12}R$ antagonists were recently development, including ticlopidine, cangrelor, ticagrelor, prasugrel, elinogrel with antiplatelet activity by antagonize $P2Y_{12}R$ in aggregation induced by mediators such as ADP, collagen, thrombin and thromboxane A2 (TXA2) [264,265]. Furthermore, metformin, wide drug used in treatment of T2DM, appear as a purinergic modulator in platelets because it avoided ADP production by decreasing activity of CD39 and CD73 enzymes [36].

On the other hand, $P2X_3R$ antagonists are antihypertensive targets, by reducing arterial pressure and basal sympathetic activity in rats with hypertension [266]. A study conducted by Pijacka et al. [266] found a potential effect of AF-219 (Gefapixant) in lowering of arterial pressure in SHR, thus representing a novel target for controlling hypertension. In addition, Sungiip et al. [267] demonstrated that MRS2578, a $P2Y_6R$-selective inhibitor, inhibited vascular remodeling in a mouse model, suggesting that $P2Y_6R$ also are a therapeutic target for the prevention of hypertension.

Modulation of adenosinergic pathway also has a crucial importance for treatment of DM and hypertension. For example, $A_{2A}R$ agonists contribute for β-cell regeneration [268], besides the $A_{2A}R$ induces blood pressure regulation by its actions on the central, vascular and renal systems [269]. While $A_{2B}R$ antagonists improve insulin secretion and reduce the inflammatory mediators and restore the insulin resistance [270]. Indeed, the $A_{2A}R$ agonist, regadenoson, a diagnostic drug for myocardial perfusion imaging, is the first selective adenosine receptor agonist to be approved, exhibited coronary vasodilator activity [269].

Thus, in view of the importance of the purinergic pathway in pathophysiological conditions, the use of selective agonists and antagonists for all purinergic receptor subtypes represent a potential therapeutic approach for DM and hypertension that need to be further explored.

5. Conclusion

As discussed in this review, several investigative studies have shown that purinergic signaling is involved in key processes associated with health and disease, especially in individuals with DM and hypertension; they work mainly in a compensatory way. The emerging concept of the purinergic system highlights the importance of cell–cell interactions among the vascular, neural, immune, and cardiovascular systems to mediate homeostasis when a patient has both DM and hypertension. In this way, the role of enzymes and purinergic receptors in the pathophysiology of DM and hypertension exhibits a dual effect that seems to indirectly alter inflammatory responses. Until now, investigations have described which ectonucleotidases exhibit activity and/or expression changes in different biological tissues in experimental models and patients with the pathologies reviewed in this study. From these findings, the next step is to determine how the catabolic activity of ectonucleotidases and purine receptors can regulate, both physiologically and pathologically, the production of proinflammatory mediators and the immune response. We consider it a promising direction to explore the specific mechanisms of the purinergic system related to progression caused by diabetes and hypertension injuries. A more comprehensive understanding of the relationship between diabetes and hypertension may help to find effective preventive and therapeutic approaches to defer or even avert micro- and macro-degenerations triggered by these diseases.

Declaration of Competing Interest

The authors report no declarations of interest.

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