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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; ATP, adenosine 5′-monophosphate; 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; DAG, diacetylglycerol; Ap3A, diadenosine triphosphate; DBP, diastolic blood pressure; 5′-NT;CD73, ecto-5′-nucleotidase; E-NTPDase, ecto-nucleotide triphosphate diphosphohydrolase; E-NPP, ecto-nucleotide pyrophosphatase; ER, endoplasmatic reticulum; eNOS, endothelial nitric oxide synthase; NTPDase1/CD39, E-NTPDase family; GABA, gamma-aminobutyric acid; GMP, guanosine monophosphate; GPCR, G-protein-coupled receptors; HASE, 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; VO2max, 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; SiR1, Sirtuin 1; SHR, spontaneously hypertensive rat; SIT, sprint interval training; STZ, streptozotocin; SSB, 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; UTP, 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

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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 Mg2+ and Ca2+ 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 purinoreceptor 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 (Mg2+ and Zn2+) 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 mitochondrion matrix, and five are present in the cytosol [54]. Ecto-5′-nucleotidase/CD73 is a Zn2+-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 (P2X1–7), which are ionotropic receptors connected to channels in the cellular membrane [62]. P2X7, 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. P2X7-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) P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11; and b) P2Y12 [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, P2Y12 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 P2Y12 [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 (A1, A2A, A2B, and A3); 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 A1 and A2A 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. A1 inhibitory receptors have been traditionally implicated with neuroprotection, while A2A 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 P2X7 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 glucose-induced insulin release [14]. Persistent inflammation in the diabetic state also is associated with the role of the P2X7R-initiated signaling cascades in the activation of the transcription factors. For example, Ca2+ influxes induced by P2X7R 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-κB 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 down-regulating phosphorylation of signal transducer and activator of transcription 3 (STAT3) in human liver cells [122].

Furthermore, Luknes 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, Luknes et al. 2008 [114], demonstrated that the hydrolysis of adenine nucleotides was augmented in human platelets in the presence of increasing glucose and fructose 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 stimulate 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 Ca2+ levels by P2YR [131,132].

In addition, there are changes in adenosinergic pathway during diabetes. Diabetic patients present elevated ADA levels [109], and
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 | [80] |
| 1989 | Wistar adult male rats | STZ (single dose – 66 mg/kg) | Pancreas | T1DM | STZ suppresses the stimulatory effect of adenosine on β-cells and reduces its vasodilator properties | [90] |
| 1992 | Wistar adult male rats | STZ (single dose – 66 mg/kg) | Pancreas | T1DM | P2Y1R agonist (ADP) stimulates 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 P2Y1R and [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<sup>–/–</sup> mice | Glucose (1 g/kg body weight; i.p.) | Pancreas | T2DM | AIR 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<sub>7</sub> 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 | [99] |
| 2009 | Male and female adult patients (60.4±8.5 years) | – | Platelets | T2DM | ↑ [ATP] and ↓ mitochondrial membrane potential | [100] |
| 2010 | Male and female adult patients (56.8±2.1 years) | – | Platelets | T2DM | ↑ ADA and 5′NT activities | [101] |
| 2010 | MIN6c4 cell line | – | – | – | ↑ expression of P2Y<sub>12</sub>R | [102] |
| 2011 | Male and female adult patients (45.6±10.4 years) | – | PBMC cells | T2DM | ↑ % of CD39<sup>−</sup> cells | [103] |
| 2013 | C57 BL/6 adult male mice and mouse Beta-Tc6 cells | – | – | – | Adenosine receptor agonists (CIB-IB-MECA, CPA, CGS2168, NECA) ↓ insulin secretion | [104] |
| 2013 | Female adult NOD-mice | – | Pancreatic islets | T1DM | ↓ A<sub>1</sub>R expression | [105] |
| 2014 | Female and male adolescents patients (mean age 14.9 years) | – | Treg cells | T1DM | Lower CD39 expression | [106] |
| 2015 | Wistar adult male rats | STZ (single dose – 55 mg/kg) | Platelets | T1DM | ↑ NTPDase, 5′-NT, E-NPP and ADA activities | [107] |
| 2015 | Female and male adult patients (mean age 48 years) | – | Treg cells | T2DM | ↑ % of CD39<sup>−</sup> cells | [108] |
| 2016 | Wistar adult male rats | STZ (single dose – 70 mg/kg) | Synaptosomes from cerebral cortex | T1DM | ↑ NTPDase activity and ↑ ADA activity. Impairment of memory | [109] |
| 2016 | Female and male adult zebrafish (Danio rerio) | 111 mM glucose solution in 5 L | Brain membranes | Hypoglycemia model | ↑ Nucleotide hydrolysis and ↑ ADA activity. ↓ Gene expressions of adenosine and adenosine receptors | [110] |
| 2016 | Wistar adult male rats | STZ (single dose – 60 mg/kg) | Platelets and synaptosomes from cerebral cortex | T1DM | ↑ ADP and AMP hydrolysis in platelets and ↑ platelet aggregation and AMP hydrolysis in synaptosomes and ↑ NTPDase, 5′-NT and ADA activities | [111] |
| 2016 | Wistar adult male rats | High-fat diet + STZ 35 mg/kg | Platelets | T2DM | ↑ ADA levels | [112] |
| 2016 | Female and male patients (mean age 58.5 years) | – | Serum | T2DM | ↑ A2AR expression in coronary arteries | [113] |
| 2016 | Adult male mice | STZ (multiple low-dose – 50 mg/kg) | Hearts | T1DM | ↑ P2X<sub>7</sub>R activation | [114] |
| 2016 | Male adult P2<sub>X</sub><sup>−/−</sup> mice | STZ (multiple low-dose – 45 mg/kg) | Pancreas | T1DM | P2X<sub>7</sub>-Knockout mice are resistant to TD1 induction and proinflammatory mediators | [115] |
| 2017 | Female and male adult patients (57 ± 6.3 years) | – | Platelets | T2DM | ↓ P2Y<sub>12</sub>R activation | [116] |
| 2017 | Wistar adult male rats | STZ (single dose – 60 mg/kg) | Serum and platelets | T1DM | ↑ NTPDase, 5′-NT and ADA activities | [117] |
| 2018 | Wistar adult male rats | STZ (single dose – 65 mg/kg) | Platelets, lymphocytes | T1DM | ↑ NTPDase and ↓ 5′-NT in platelets | [118] |
| 2018 | Wistar adult male rats | STZ (single dose – 55 mg/kg) | Synaptosomes and total cerebral cortex | T1DM | ↑ NTPDase activity and A<sub>1</sub>R density | [119] |
| 2018 | – | – | CD8<sup>+</sup> effector T cells | T1DM | ↑ A<sub>1</sub>R and P2X-R density and Up regulation of P2X-R | [120] |

(continued on next page)
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 A₁ receptor expression in pancreatic islets may contribute to the T1DM pathology in NOD-mice, and the activation of A₁ and A₂A receptors augmented insulin secretion, while the A₃ 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 A₁ receptor agonists is sufficient to stabilize glucose levels and increase sensitivity to insulin in tissues [134], while diminished A₁ receptor expression in pancreatic islets may contribute to the T1DM pathology [103]. Thus, the regulatory role of A₁ 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 A₂A receptor is related to β cell proliferation, regeneration, and survival [73].

Additional A₂A and A₂B receptor activation protects islet grafts from T cell-mediated injury [124]. The A₃ receptor agonist, CI-IBMECA, potentiates glucose-induced insulin secretion from MIN6 insulinoma cells possibly through transient Ca²⁺ 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 nucleotide(s) is related to blood vessels and the cardiovascular system

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

Table 1 (continued)

| Year | Subjects | Induction | Tissue / cell | Diabetes model | Outcomes | References |
|------|----------|-----------|--------------|----------------|----------|------------|
| 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 P2X₇R | [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 | – | – | – | A₁R agonist, CI-IBMECA, potentiated glucose-induced insulin secretion | [118] |

* Hypoglycemiants therapy (insulin for T1DM, metformin/glibenclamide for T2DM).
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 A1R, P2X7-R, and P2Y12-R [136]. Indeed, the P2Y12-R modulating Ca2+ 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 P2Y12-R, 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 P2Y12-R and P2Y1-R [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 P2Y12-R or a P2Y11-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, P2Y12-R-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 constriction 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 P2Y12-R was observed in swine with metabolic derangement (DM and dyslipidemia) [148]. And Up4A induces aortic constriction, which partially requires the activation of P2X7-R 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. P2X7 plays a crucial role in regulating vascular function in diabetes: In diabetic rats, resting vascular reactivity increased ATP release; ATP then bound to P2X7, 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 P2Y12 [153]. Hu et al. [112] demonstrated that P2Y12 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 P2Y1 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 A2B receptor is relevant because it decreases platelet adhesion and activation by antagonizing ADP-mediated effects via P2Y12 [154]. Indeed, A2B receptor upregulation enhances coronary flow in diabetic hearts [110]. On the other hand, A1 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 A2B receptors [14]. A2B receptors mediate 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 A1 and A2 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 peripheral cells, DM is associated with dysfunction in neurotransmission systems, including the purinergic system and memory impairment [96].
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 P2X7 and promotes the influx of intracellular Ca2+, 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 P2X7 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 vasoconstraining 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 coagulation 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 P2X7 [24], while an increase in the ADA activity reduces anti-inflammatory Ado levels [37].

In addition, a recent study revealed that P2X7-R 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 predispose to T1DM in murine model [11]. P2X7 is upregulated on CD8+ effector T cells in patients with T1DM, and P2X7 blockade reduces the CD8+ T cell–mediated autoimmune response in vitro and delays diabetes onset in NOD mice [114]. There are more P2X7+ 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 non-communicable 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) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg, or antihypertensive adhesion treatment [6]. Briefly, BP is controlled by the relationship between circulating 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—only with 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 Ca2+/calmodulin system elevate intracellular Ca2+ 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 P2X7-R to constrict vascular smooth muscle. Using human samples, in vitro strategies, and a rat model, Helinius 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 P2X1, P2X4, P2X6, P2Y1, P2Y2, P2Y6 and P2Y12 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 P2Y2R and/or P2Y6R [189], and P2Y2R activation is linked to mechanisms that contribute to decreases BP [190]. In contrast, impaired UTP-induced carotid arterial relaxation endothelium-dependent in SHR arteries through impaired P2Y2R, in the contribution of other receptors, as P2Y1R and P2Y6R. Thus, occurs the UTP-mediated vasomotor response in hypertension-associated vascular complications [191]. In addition, mice with endothelium-specific P2Y1R 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 P2Y1R 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 P2X1R and the vasoactive effect of Up4A was impaired in aortas isolated from Ang II-infused hypertensive mice. Thus, the vascular P2X1R 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 P2Y1R [196]. Therefore, Up4A-P2R signalling implies a crucial role in cardiovascular complications associated with hypertension.

In relation to P2X1R, this receptor plays a key role in the development of hypertension via increased inflammation [197]. Antagonism of P2X1R reduces BP in Ang-II-treated rats [198]. Interestingly, genetic alterations in a region of the P2X1R and P2X4R genes affect the BP in humans, and drugs that modulate P2X1R 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 hypoxia-sensitive conditions in one of the mechanisms by which Up4A activates NFAT expression dependent in part on the activity of NF-κB [201]. Activators of Gα-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, Tofilovic 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 [209].

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 A2BR knockout mice was observed an increase in endothelial cells proliferation, as well as in smooth muscle hypertrophy. Perhaps, Ado acts as A2AR triggers an important regulatory mechanism to protect against development of hypertension [210]. Similarly, endothelial cell proliferation and angiogenesis also is mediated by A3AR, 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 A3AR, 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-R in the kidneys of diabetic rats subjected to aerobic training on a treadmill. The authors found increased P2X-R expression in control animals. Exercise reduced this alteration and thereby might represent an adjuntive treatment to slow the progression of diabetic nephropathy [219]. Taghizadeh et al. [220] evaluated the expression of the P2Y1R 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 (VO2max) compared with moderate intensity exercises [227]. Bahmanbegliou 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 vasodilatation and, thus, mediate the hypertensive 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 sympatholitic 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 P2Y1R between the groups before and after training. However, the training reduced the vasodilatory response to ATP and increased the...
skeletal muscle P2Y₂R 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. A2AR 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 purinoreceptor 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 autophagosome 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, anti-hypertensive, 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 properties 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 glyco-sylated 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 A2A 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

Nucleotides mediate the effects of vascular tone, inflammation and thrombosis by binding with specific receptors. Antithrombotic actions are attributed with P2Y₁R antagonism as a complement to current P2Y₁₂R antithrombotic strategies. Furthermore, the P2X₇R is linked to vasoconstrictor mechanisms [259], while actions mediated by P2Y₂R are involved with the regulation of angiogenesis [260]. In contrast, ADO plays antithrombotic effects by A₂AR, A₂BR and A₃R [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 P2Y₁₂R antagonist, is used clinically to inhibit platelets aggregation for thrombosis and stroke [163,263]. Similarly, others P₂Y₂R antagonists were recently development, including ticlodipine, cangrelor, ticagrelor, prasugrel, etinogrel with antiplatelet activity by antagonize P₂Y₁₂R 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, P₂X₇R 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 P₂X₇R-selective inhibitor, inhibited vascular remodeling in a mouse model, suggesting that P₂X₇R 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, A₂AR agonists contribute for β-cell regeneration [268], besides the A₂AR induces blood pressure regulation by its actions on the central, vascular and renal systems [269]. While A₂PR antagonists improve insulin secretion and reduce the inflammatory mediators and restore the insulin resistance [270]. Indeed, the A₂AR 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 catalytic 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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