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Review

Anti-Inflammatory Effects of Peripheral Dopamine

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Abstract: Dopamine is synthesized in the nervous system where it acts as a neurotransmitter. Dopamine is also synthesized in a number of peripheral organs as well as in several types of cells and has organ-specific functions and, as demonstrated more recently, is involved in the regulation of the immune response and inflammatory reaction. In particular, the renal dopaminergic system is very important in the regulation of sodium transport and blood pressure and is particularly sensitive to stimuli that cause oxidative stress and inflammation. This review is focused on how dopamine is synthesized in organs and tissues and the mechanisms by which dopamine and its receptors exert their effects on the inflammatory response.

Keywords: immune cells; signaling pathways; kidney; mesenteric organs; pro-inflammatory factors

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1. Introduction

In addition to the central nervous system, dopamine (DA) is produced locally in several peripheral organs and in different types of cells and influences numerous functions, including gastrointestinal motility, metabolic homeostasis, hormone release, sodium balance, and blood pressure [1–3]. In the periphery, under normal conditions, very little DA is released from the adrenal medulla or the sympathetic nerves into the circulation; circulating concentrations of DA in the free form, ranging from 0 to 30 pg/mL (195.8 pmol/L) in humans [4], are too low to have any physiological effect. However, significant amounts of DA are produced by organs other than the brain. In humans and laboratory animals, at least 90–95% of DA in the plasma circulates in the sulfoconjugated form. DA is sulfoconjugated before entering the bloodstream and its formation is dependent on the intracellular synthesis of L-DOPA and DA in non-adrenergic cells and in the uptake of circulating L-DOPA [5]. The lung, mesentery, and other organs and cell types contribute to the total body production and metabolism of DA [6]. Peripheral production of DA results in urine concentrations of DA and its metabolites that are higher than those of norepinephrine (NE) and its metabolites, underlying the importance of the dopaminergic system and supporting the notion that DA in the periphery acts as an autocrine/paracrine hormone that is rapidly inactivated by sulfoconjugation [5,7].

In addition to the functions of DA mentioned above, DA and dopaminergic drugs that bind to their receptors have been demonstrated to regulate the immune response as well as the inflammatory reaction [8]. Both in vitro and in vivo studies suggest that DA can suppress the inflammatory reaction. Retained during evolution, the peripheral dopaminergic system is beginning to be recognized as an endogenous anti-inflammatory system. DA acts via two subfamilies of G-protein-coupled receptors, namely D1-like (D1R and D5R) and D2-like (D2R, D3R, and D4R) receptors. All the DA receptor subtypes are differentially expressed in tissues depending on their physiological function. The mechanisms underlying these effects and actions are starting to be recognized and emerging evidence suggests that they can be tissue-specific. This review focuses on the effects and mechanisms of peripheral DA on inflammation.

1.1. Dopamine and Immunomodulation

Several studies have shown that DA functions as an immunomodulatory regulator and that this regulation is an important part of the healthy immune function. More recent studies have reported DA-induced changes in the functions of lymphocytes, macrophages, monocytes, and neutrophils. All types of immune cells produce dopamine at low levels and dopamine receptors are expressed on T cells, B cells, neutrophils, eosinophils, natural killer (NK) cells, dendritic cells, macrophages, microglia, and monocytes [9–12]. Acting in an autocrine/paracrine manner, DA modulates the functions of immune cells through D1-like and D2-like receptors. These receptors have been reported to regulate the activation, inhibition, and proliferation of immune cells and their functions [13–21]. The ability of DA to inhibit the production of reactive oxygen species by human polymorphonuclear leukocytes and their migration is dependent on D1-like receptors' activation, in particular the D5R [17].

The administration of dopexamine, a synthetic analog of dopamine with β2 adrenergic properties, in patients undergoing cardiopulmonary bypass reduces circulating TNFα levels and leukocyte count [22]. Dopexamine also decreases the number of leukocytes adhering to the vascular endothelium and plasma TNFα levels in a rat model of experimental sepsis [23]. DA also inhibits the activation of T cells, resulting in the downregulation of their proliferation and secretion of the cytokines IL-2, IL-6, IL-4, IFN-c, and IL-4 [24]. However, the D1-like receptor antagonist SCH23390 has been shown to attenuate Th17-mediated immune diseases such as experimental autoimmune encephalomyelitis [25], autoimmune diabetes in non-obese diabetic mice [26], and nephrotoxic serum nephritis [27]. These findings indicate that the effects of DA on T cells are dependent on the concentrations of DA or DA agonists present, the type and subtypes of T cells, and more importantly on the state of T cell activation [14–16,18–20]. In peritoneal macrophages, DA inhibits the lipopolysaccharide (LPS)-stimulated production of IL-12p40 and increases the production of the anti-inflammatory cytokine IL-10 [28]. However, in contrast to these inhibitory effects of DA on inflammation in these cells, dopexamine, a synthetic analog of dopamine with D1-and D2-like receptor and β2-adrenergic properties increased circulating TNFα, soluble TNF receptor, and leucocyte count in humans [22]. Nevertheless, there is agreement that DA inhibits NLRP3 inflammasome activation in macrophages. In LPS-treated bone marrow-derived macrophages, treatment with DA at high concentrations, before a challenge with nigericin, an NLRP3 stimulant, negatively regulates the NLRP3 inflammasome activation through D1R signaling via cyclic adenosine monophosphate (cAMP), which promotes the ubiquitination and degradation of the inflammasome [13]. Moreover, DA at high concentrations (>100 μM) suppresses pro-inflammatory mediators (IL-1β and IL-18 but not TNFα) and the NLRP3 activation in macrophages stimulated with LPS [29]. Furthermore, DA and D1R signaling ameliorates, in vivo, monosodium urate crystal-induced peritoneal inflammation, neurotoxin-induced neuroinflammation, and LPS-induced systemic inflammation all inflammatory pathologies that mediated by the NLRP3 inflammasome, although these effects are only observed at doses of DA higher than 100 μM [13] that may activate receptors other than DA, such as α1, α2, and β-adrenergic receptors [2].

The role of D2-like receptors, relative to D1-like receptors, on immune cells appears to be less controversial. Either D2-like agonist- or cell-specific D2R activation attenuates inflammation in rodent models of sepsis or chronic neuroinflammation [10,11]. Three D2-like receptor agonists, pramipexole (D3R > D2R), bromocriptine (D2R = D3R > D4R), and pergolide (D3R > D2R > D4R > D5R > D1R), have also been shown to possesses significant anti-inflammatory activity in several models of inflammation in rodents, reducing tissue injury, neutrophil infiltration, and subcutaneous edema [30,31]. D2-like receptors appear to be more important than D1-like receptors in regulating T cells. In T lymphocytes stimulated with concanavalin A, quinpirole, a D2-like receptor (D3R = D4R > D2R) agonist, upregulated the expression of specific transcription factors and cytokines of Th2 and Treg but downregulated the expression of specific transcription factors and cytokines of Th1 and Th17, promoting the differentiation of T lymphocytes to an anti-inflammatory

phenotype [32]. In isolated bone marrow-derived macrophages, treatment with the D2R agonist quinpirole inhibited M1 macrophage polarization, decreased NADPH oxidase-mediated oxidative stress and NF-κB, and it also decreased the activation of the NLRP3 inflammasome, effects that were lost after specific deletion of the D2R in bone marrow macrophages [33]. However, in both immortalized and primary macrophages in culture, pretreatment with the D2R antagonist haloperidol (D4R > D2R = D3R = D1R > D5R) inhibited the activation of NF-κB induced by LPS and decreased CD80 expression and the secretion of pro-inflammatory cytokines (IL-1β, IL-6, and IL-12p40) [34]. These effects (CD80 and IL-6) were also attenuated by a different D2-like receptor antagonist, L750.667, that may be selective to D4R [35]. Meanwhile, a D1-like receptor antagonist had no effect, suggesting actions via D2-like receptors [34]. For an in-depth review of the role of dopamine on the immune system please see ref. [8].

1.2. Anti-Inflammatory Effects of Dopamine in Peripheral Organs, Tissues, and Cells

Inflammation is a complex process that is necessary to defend organisms from pathogens or injury. However, it becomes harmful when it occurs in the absence of noxious stimuli or is not controlled in a timely manner. In organs and tissues, inflammation depends on two major factors, the intrinsic response of specific cells in the tissue and the infiltration of immune cells into those tissues. The interrelations of these factors can be tissue-specific.

1.2.1. Dopamine in Abdominal Organs

Abdominal organs (mesentery, gastrointestinal tract, spleen, and pancreas) produce a substantial portion of the total DA produced in the body [36–38]. Not only can some enteric neurons synthetize and release DA [36,37] but they can also stimulate tyrosine hydroxylase (TH), the enzyme that synthesizes DOPA from tyrosine. Other enzymes in the DA synthetic pathway are expressed in many cells in the abdominal organs (Figure 1). In human and experimental animals, DA synthesis has been reported in parietal cells and other epithelial cells in the stomach [38].

DA is abundant in the mucosal cell layer of the intestine; the epithelial cells of the intestinal mucosa have abundant aromatic L-amino acid decarboxylase (AADC) and are capable of the uptake of circulating DOPA to produce DA, particularly in the jejunum. In the gastrointestinal tract, DA has marked anti-inflammatory properties mediated by the suppression of interleukins (IL-1β, IL-6) and TNFα, as well as inhibition of the activation of the NLRP3 inflammasome, that is mediated by the D1R [13] and D2R [39]. The D2-like receptor agonist, bromocriptine (D2R = D3R > D4R), ameliorated a drug-induced inflammatory bowel disease and decreased its mortality, whereas treatment with the D2-like receptor antagonist domperidone (D2R > D3R), worsened the condition and increased the mortality rate [40]. By contrast, D3R deficiency attenuated gut inflammation in mice caused by dextran sodium sulfate by decreasing IL-10 production and gut growth [41], indicating that dopamine exerts its protective effect in drug-induced gut inflammation via the D2R. The concentration of DA in the inflamed mucosa of ulcerative colitis and Crohn's disease patients was markedly lower than in controls. This resulted in significant reductions in DA/L-DOPA tissue ratios, which is a rough measure of aromatic L-amino acid decarboxylase activity [42]. Treatment with D2-like receptor antagonists quinpirole (D3R = D4R = D2R) or cabergoline (D2R = D3R) ameliorated the colonic lesion in two animal models of ulcerative colitis via downregulation of AKT phosphorylation and c-Src [43].

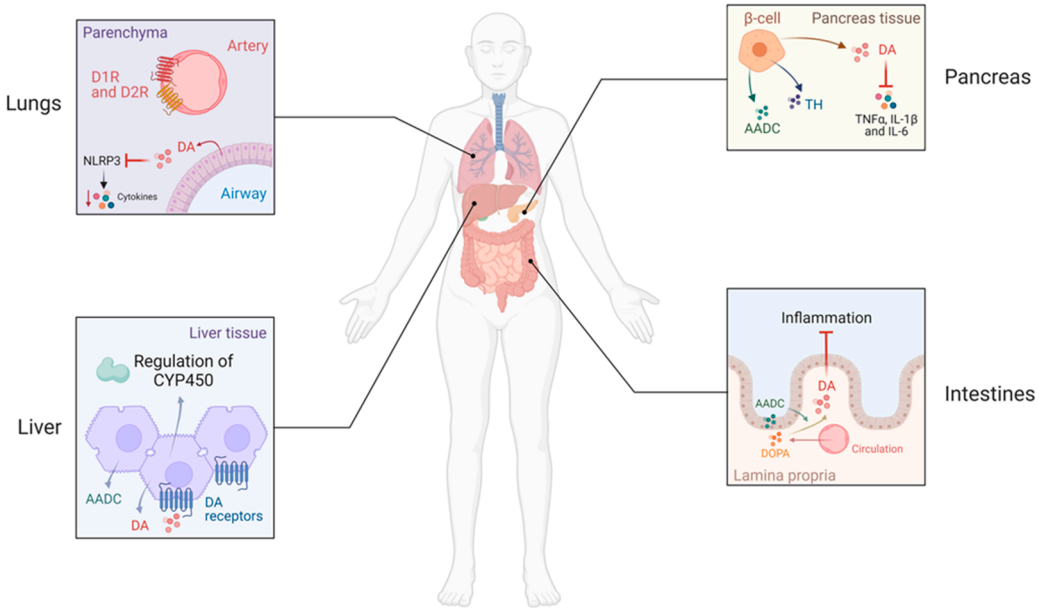

Figure 1. Peripheral dopamine (DA) production and actions. In the lung, alveolar type II epithelial cells can synthesize DA, which attenuates lung tissue injury, neutrophil infiltration, and inhibits inflammatory cytokine response through inhibition of NLRP3-signaling pathways. DA may also modulate ventilation by acting on dopamine D1 (D1R) and D2 (D2R) receptors in the arteries of the lung. In the liver, aromatic l-amino acid decarboxylase (AADC) is expressed, and DA is produced by hepatocytes. D2R can modulate the regulation of components of the cytochrome P450 (CYP450). Moreover, DA may protect the liver from acute injury. In the pancreas, DA is synthesized mainly in β-cells that intracellularly express TH and AADC and regulate insulin production in these cells. DA reduces the increased expression of inflammatory cytokines (TNFα, IL-1β, and IL-6) induced by cholecystokinin in acute experimental pancreatitis. In the intestines, DA is abundant in the mucosal cell layer; the epithelial cells of the intestinal mucosa are rich in AADC and circulating DOPA is taken up to produce DA. DA reduces the inflammation in human inflammatory bowel disease.

The pancreas is an important source of non-neuronal DA and L-DOPA. DA is synthesized in α- and β-cells, which express TH and AADC and regulate glucagon and insulin production in these cells [44]. Rat-derived lines of pancreatic α -cells produce L-DOPA from tyrosine but not DA, while β-cells synthesize DA by the uptake of L-DOPA [45]. DA has an important role in protecting the pancreas and intestinal mucosa from injury, e.g., pancreatitis [46–51]. DA-synthesizing enzymes are increased in the pancreas in models of acute experimental pancreatitis [49,50]. DA is an effective treatment for this experimental condition; it reduces the cholecystokinin-induced increase in the expression of inflammatory cytokines (TNFα, IL1β, and IL-6). These effects are D2R-mediated through PP2A-dependent Akt/NF-κB signaling [50]. In other animal models of acute pancreatitis, D2R also attenuates acinar cell necroptosis. In addition, activation of the D2R inhibits oxidative stress-induced macrophage polarization, NF-κB activation, and the NLRP3 inflammasome. Activation of D2R also reduces trypsinogen activation and HSP70 upregulation, thus contributing to its beneficial effects on the disease, suggesting that activation of D2R may be a pharmacological treatment for acute pancreatitis [51]. DA, vesicular transporters, and DA receptors are expressed in the spleen [52]. Indeed, L-DOPA and DA increased the proliferation of splenic lymphocytes that were stimulated with concanavalin A or anti-CD3 but downregulated the number of IFNϒ producing cells [53]. All five DA receptors have been detected in splenic natural killer (NK) cells and modulate their toxicity by regulating the cAMP-PKA-CREB signalling cascade. D1-like receptor activation enhances NK cell cytotoxicity, while activation of D2-like receptors supresses NK cells [54]. In diabetic septic mice, fenoldopam, a D1-like receptor agonist, attenuated hyperglycemia and systemic inflammation through inhibition of p65NF-kB phosphorylation in the spleen [55]. Fenoldopam inhibits TNFα production

in splenocytes even at high concentrations of glucose and inhibits p50NF-kB1 phosphorylation and the canonical NF-kB pathway by inhibiting p65RelA, without affecting the non-canonical NF-kB proteins [55] (Figure 2).

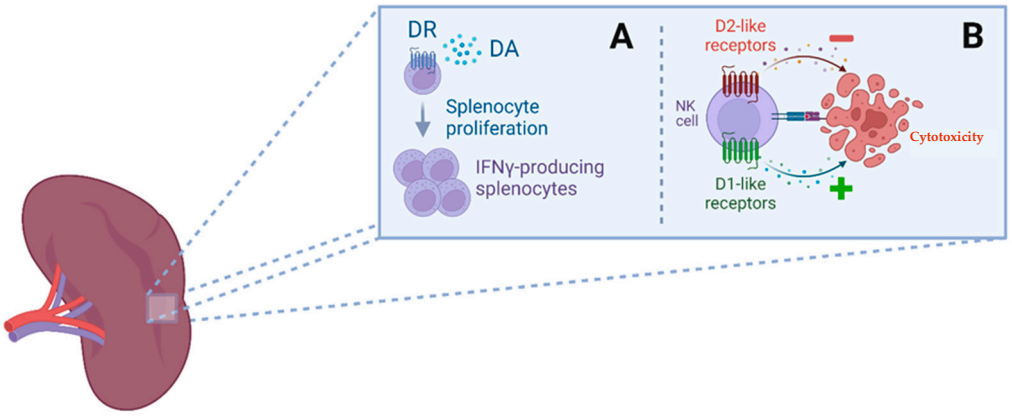

Figure 2. Dopamine (DA) actions in the spleen. (**A**) DA acts on dopamine receptors (DR) and increases the proliferation of IFNγ-producing splenocytes stimulated with concanavalin A (ConA) or anti-CD3. (**B**) All five DA receptors have been detected in splenic NK cells. D1-like receptors (D1R and D5R), when stimulated by DA, lead to increased cytotoxicity. By contrast, when DA acts on D2-like (D2R, D3R and D4R) receptors, it decreases NK cell-mediated cytotoxicity. Both actions, although opposite of each other, are due to the modulation of the cAMP-PKA-CREB signalling pathway through DA receptors.

1.2.2. Dopamine in the Liver

Hepatocytes are rich in AADC and synthesize DA that may protect the liver from acute injury. In mice exposed to LPS or LPS/d-galactosamine (D-Gal), a model of acute liver injury, treatment with DA or the D2-like receptor agonist rotigotine (D2R > D3R > D4R > D5R > D1R) reduced the number of abnormal histologic lesions, decreased plasma aminotransferases, and increased survival rates [39,56]. DA also suppressed in the liver the production of TNFα induced by LPS/D-Gal and decreased apoptosis in the treated mice [57]; this may also involve the production of reactive oxygen species [58] and α2-adrenergic receptors [59]. A selective D1-like receptor agonist, A68930 (D1R = D5R), suppressed immune cell-mediated hepatitis in mice by inhibition of IL-4 and interferon γ through the PKA pathway [60]. In liver cancer, fisetin, which can act as a D2R agonist, inhibited TGF-β1 secretion and reduced epithelial mesenchymal transition not only by downregulating VEGFR1, p-ERK1/2, p38 and pJNK signaling pathways, but also by inducing apoptosis of liver cancer cells by activating caspase-3, indicating that DA may inhibit the growth of liver cancer [61]. Moreover, DA receptors, specifically D2R, regulate cytochrome P450 (CYP) enzymes in hepatocytes by activation of the pathway insulin/PI3K/AKT [62]. CYP enzymes from the liver are crucial in the metabolism of numerous environmental toxic substances [62]. Thus, DA receptors in hepatocytes may be protective against the toxicity and carcinogenicity of numerous substances (Figure 1).

1.2.3. Dopamine in the Lung

Endogenous DA levels are high in the lungs [63]. The lung expresses AADC and synthesizes DA mainly in alveolar type II epithelial cells and in pulmonary neuroendocrine cells [64]. Pulmonary arteries express both D1R and D2R [65–67]; these receptors are also expressed in the carotid bodies of experimental animals [68,69], suggesting that DA has a role in the control of ventilation [70] and that DA in this organ is involved in a number of pulmonary functions, as well as in anti-inflammatory effects (Figure 1). DA may improve respiratory muscle function and has been used for treating conditions such as bronchial asthma and chronic obstructive pulmonary disease to induce bronchodilation because D2R activation decreases pro-inflammatory reflex responses and inhibits neurogenic in-

flammation [63,71,72]. D1-like receptor stimulation with fenoldopam in macrophages, human monocytes, and alveolar epithelial cells, but not in neutrophils, decreases IL-1β via AMPK activation and reduces in vivo LPS acute lung injury through mechanisms involving inhibition of TLR4 in macrophages and a decrease in paracrine IL-1β-induced adverse signaling in alveolar epithelial cells [73]. However, D1R increases mucus production that can worsen airway obstructive symptoms [74]. However, dopamine has been shown to ameliorate LPS-mediated pulmonary edema and decrease myeloperoxidase activity, an index of neutrophil infiltration that may be related to the D2R [75]. These studies highlight the importance of D1-like and D2-like receptor signaling pathways in reducing acute lung injuries that are related to the inhibition of immune cell activation.

1.2.4. Dopamine in the Cardiovascular System

DA receptors in the heart participate in myocardial hypertrophy and fibrosis. Dopamine receptors are expressed in atrial and ventricular walls, as well as in coronary arteries [76]. In the human heart, D1R, D2R, D4R, and D5R are present in the myocardium and epicardium, but so far there are no reports of D3R expression in this organ [77]. The specific role of each DA receptor in the human heart still needs to be determined. D1R signaling downregulated the NLRP3 inflammasome in cardiomyocytes treated with doxorubicin and reduced cardiac injury and fibrosis in doxorubicin-treated mice by also suppressing the NLRP3 inflammasome in the heart [78]. In cultures of neonatal rat ventricular myocytes, D2-like receptor stimulation with bromocriptine inhibited the angiotensin II-induced hypertrophy of neonatal rat ventricular myocytes [79] and decreased apoptosis in myocytes subjected to ischemia/reperfusion injury [80]. In a rat model of cardiac hypertrophy, bromocriptine decreased the hypertrophy index by acting on the D2R [81]. D2R signaling is involved in the cardioprotective effects of ischemic preconditioning and postconditioning. Ischemia/reperfusion in the heart increased D2R expression; D2R expression was further increased by conditioning and additional treatment with the D2-like receptor agonist bromocriptine, which improved cardiac function, resulting in a more pronounced reduction in apoptosis, cardiomyocyte damage, and myocardial infarct [82–85]. In healthy C57BL/6J mice, the activation of D3R with pramipexole was capable of reducing cardiac hypertrophy after morphine administration [86]. However, *Drd3*$^{-/-}$ mice had increased interstitial fibrosis and expression of collagen type I which increased with age, indicating that D3R has a role in the development of aging-related remodeling, cardiac fibrosis, and dysfunction in mice [87]. In ex vivo and in vitro experiments, activation of D4R with PD168077 improved cardiac function in the ischemia/reperfusion-injured heart, reduced infarct size, and enhanced the viability of cardiomyocytes impaired by this injury by increasing PI3K and AKT phosphorylation [88].

In endothelial cells, sumanirole, a specific D2R agonist, has antioxidant, anti-inflammatory, and antiapoptotic effects, counteracting those induced by bradykinin, a proinflammatory B2R-activating peptide. The co-stimulation of both B2R and D2R receptors regulated the expression of markers of apoptosis such as Bcl-2, Bcl-xL, and Bax and inhibited the release of IL-6 and endothelin-1 [89]. In human umbilical vein endothelial cells, the D2-like receptor agonist rotigotine (D2R > D3R > D4R > D5R > D1R) inhibited NF-κB activation and reduced its reporter activity, exerting anti-inflammatory actions [90]. DA, receptor not determined, also regulated the interaction of leukocytes and the endothelium, decreasing the transendothelial migration of leukocytes and the expression of ICAM-1 and E-selectin in endothelial cells and attenuating the chemoattractant effect of IL-8 [91,92].

1.2.5. Dopamine in Adipose Tissue

Human adipocytes express four DA receptor subytpes (D1R, D2R, D4R, and D5R), and have been shown to be involved in cytokine/adipokine release, especially during adipogenesis [93,94]. D2R receptors seem to mediate the inhibitory effect of DA on adipocyte prolactin gene expression and release, while D1-like receptors decrease adiponectin, leptin, and IL-6 production and release [93]. However, it also has been reported that D2R activation

could upregulate the production of leptin and IL-6 in adipocytes [95]. In that sense, it has been proposed that DA is likely a key signaling molecule connecting adipocytes, immune cells, and sympathetic nerve terminals, playing a role in immune–metabolic diseases such as obesity [94]. The role of DA is not limited to the white adipose tissue. D1-like receptors in brown adipocytes increase oxygen consumption rates and mitochondrial mass through p38 MAPK phosphorylation [96]. Nevertheless, the relevance of the effect of DA and its receptors on brown adipose tissue is still controversial, since the acute peripheral administration of a D1-like receptor agonist SKF38393 in mice only transiently increased brown tissue temperature after injection, while there was no sustained difference in temperature after repeated daily administration [97]. Moreover, these effects could be attributed to indirect consequences of DA receptors activation in the vascular system via peripheral action during administration of DA receptor agonists [98]. Future studies are needed to understand the role of local DA receptors in adipose tissue.

1.2.6. Dopamine in Bone and Connective Tissues

DA reduced the osteolysis induced by titanium particles, as well as the formation of osteoclasts and the expression of genes related to osteoclastogenesis, and alleviates peri-implant osteolysis, a common complication of prostheses implantation. Peri-implant osteolysis is generated by the recruitment of fibroblasts, osteoclasts, osteoblasts, and immune cells that produce significant amounts of cytokines and chemokines, resulting in stimulation of the formation of osteoclasts and bone reabsorption. [99]. The DA effect was reversed by haloperidol, a D2-like receptor antagonist (D4R > D2R = D3R = D1R > D5R), while the D1-like-receptor antagonist SCH23390 had no effect [99]. D2R agonism in mice with collagen-induced arthritis decreases the signs of inflammation and the imbalance of Treg cells. The D2-like receptor agonist quinpirole (D3R = D4R = D2R) decreased the expression of Th17-related cytokines, IL-7 and IL-22, and increased Treg anti-inflammatory cytokines in mice with arthritis induced by collagen [100]. By contrast, mice lacking the D2R presented with more severe limb inflammation, more expression of IL-17 and IL-22, and a downregulated expression of anti-inflammatory cytokines when compared to wild-type mice. However, in mice lacking the D1R, relative to wild-type mice, collagen-induced arthritis did not alter limb inflammation [100].

1.2.7. Dopamine and the Kidney

The kidney produces DA that is not further transformed to norepinephrine. The glomerulus freely filters DA in the plasma, however, the concentration of free DA in the plasma is usually in the low picomolar range [101,102] and cannot contribute significantly to urinary dopamine, the concentrations of which are in the micromolar range [103–106]. The contribution of renal dopaminergic nerves is less than 30% of the kidney production of DA [103,107–113]. The main source of renal DA is from the decarboxylation of L-DOPA [114–121]. For the most part, plasma L-DOPA is produced in tissues innervated by the sympathetic nervous system and reflects the turnover of catecholamines [122–125]. The renal tubules take up L-DOPA from either the circulation or glomerular filtrate and it is converted to DA by AADC [119–121]. L-DOPA uptake is mediated by LAT2, an L-type amino acid transporter type 2, and occurs mainly in the proximal tubule; DA production from L-DOPA could not be detected in isolated glomeruli [121]. The renal production of DA relies heavily on how the expression of LAT2 (SLC7A8) is regulated [126–129].

In the kidney, DA has anti-inflammatory effects. DA decreases the infiltration of monocytes and the expression of IL-6, and improves renal function after transplantation, in brain-dead rats, a condition associated with severe inflammation in end-organ targets [130]. Mice with intrarenal DA deficiency have increased infiltration of inflammatory cells and oxidative stress [131]. Moreover, decreased renal DA production is associated with increased detrimental effects of angiotensin II on renal injury, as well as worsening of diabetic nephropathy [132,133].

The effect of DA on oxidative stress in the kidney has special importance, as the imbalance between the generation of oxidants and antioxidants is a key player in the pathogenesis and progression of hypertension and the development of renal damage [134–137]. Renal D1R function is impaired by oxidative stress. Inhibition of the redox-sensitive transcription factor nuclear factor E2-related factor 2 in mice resulted in oxidative stress, renal functional impairment, and elevated blood pressure [138,139]. Different NADPH oxidase (NOX) homologs and their respective regulatory subunits are involved in the pathogenesis of essential hypertension and subsequent renal damage [137]. NOX1 overexpressing mice have impaired endothelium-dependent relaxation and reduced NO bioavailability [140], similar to NOX2 overexpression [141]. D2R decreases oxidative stress in part by reducing the renal expression of NOX isoforms and activity of NADPH oxidase by increasing the expression of two antioxidant factors, paraoxonase 2 and sestrin 2 [142–144]. D1R and D5R also contribute to the inhibition of renal NADPH oxidase activity and decrease reactive oxygen species production via PKA/PKC cross talk [145,146] and PLD2 [147,148], respectively. The D5R also interacts with peroxredoxin-4 to reduce renal oxidative stress and inflammatory factors in mice [149].

DA and its receptors also interact with components of the renin-angiotensin system (RAS) in the kidney in a reciprocal fashion. Angiotensin II receptor (AT1R) activation can decrease renal DA effects by inhibiting the extraneuronal (e.g., renal tubule cells) uptake of DA [150], while D1R and D3R increase renin secretion by juxtaglomerular cells [151,152]. D1-like and D2-like receptors can cause the downregulation of the AT1R in renal proximal tubule cells [152–157]. These interactions in the kidney are particularly important for the regulation of blood pressure, as the impaired interaction of the receptors from both systems may play a role in the pathogenesis of genetic hypertension [154]. Nevertheless, these effects are not restricted to the classical RAS axis, as angiotensin-(1-7) increases intrarenal DA production [158].

The D2R plays an essential role in renal homeostasis. In mice, global D2R deletion increases renal inflammation and blood pressure; apocynin treatment, which decreased oxidative stress, normalized blood pressure but did not affect the expression of inflammatory factors [142]. In uninephrectomized mice, selective renal downregulation of *Drd2*, using siRNA technology for one week, increased the renal expression of proinflammatory factors, injury markers, and blood pressure, while in intact mice the same procedure in only one of the kidneys increased inflammation and markers of renal injury in the treated kidney but did not increase blood pressure [142]. However, long-term (4 weeks) renal-selective silencing of *Drd2* in only one of the mouse kidneys not only increased renal expression of proinflammatory and profibrotic factors but also increased blood pressure and decreased renal function [159]. Renal rescue of *Drd2* function in these mice using retrograde ureteral infusion of adeno-associated virus (AAV9) vectors, carrying *DRD2* cDNA, reduced the expression of pro-inflammatory factors and kidney injury, preserved renal function, and normalized systolic and diastolic blood pressures, thus demonstrating that the primary D2R effect is anti-inflammatory and antifibrotic, and renal damage induced by defective D2R function is the cause and not the result of hypertension [159,160]. The protective effects of the D2R in the kidney were also shown by the renal selective overexpression of the receptor, which mitigated the increase in pro-inflammatory and profibrotic factors, decrease in renal function, and increase in blood pressure in mice subjected to ischemia/reperfusion injury [160].

Specific deletion of the D2R in the renal proximal tubule in male mice increased the expression of pro-inflammatory and profibrotic factors in the kidney, as well as blood pressure [161] (Figure 3). Cells of the renal tubule produce pro-inflammatory and anti-inflammatory cytokines that are secreted across the apical and basolateral membranes of renal tubule cells and contribute to the development and progression of glomerular and tubular injury [162–164]. D2Rs are expressed in renal proximal and distal tubule cells. The anti-inflammatory effects of D2R are mediated in part by modulation of the AKT (protein kinase B) pathway [165]. In mouse renal proximal tubule cells, D2R downregulation increases

pro-inflammatory factors and NF-kB reporter activity due to the increased phosphorylation and activity of AKT. By contrast, D2R stimulation decreases the expression of inflammatory factors and AKT phosphorylation. Inhibition of protein phosphatase 2A (PP2A) that dephosphorylates AKT reproduces the effects of D2R downregulation, indicating that decreased phosphatase activity is involved in the inhibitory effect of D2R on inflammatory factors [165]. The D2R facilitates AKT inactivation by a G-protein-independent, arrestin-dependent pathway, promoting the formation of a signaling complex with β-arrestin 2, AKT, and PP2A, leading to AKT dephosphorylation and inactivation by PP2A [166]. Glycogen synthase kinase β (GSK3β), a key signaling kinase, is also regulated by AKT through phosphorylation. GSK3β is constitutively active in its non-phosphorylated form, whereas AKT-induced phosphorylation inactivates GSK3β [167]. Active GSK3β phosphorylates β-catenin, a transcriptional co-activator of Wnt, target genes and undergoes proteosomal degradation. However, inactivation of GSK3β activity results in β-catenin translocation to the nucleus and the initiation of the transcription of genes of the Wnt pathway, in particular, Wnt3a [168]. This positive crosstalk between the D2R and Wnt/β-catenin signaling pathways regulates cell proliferation and improves the renal response to injury.

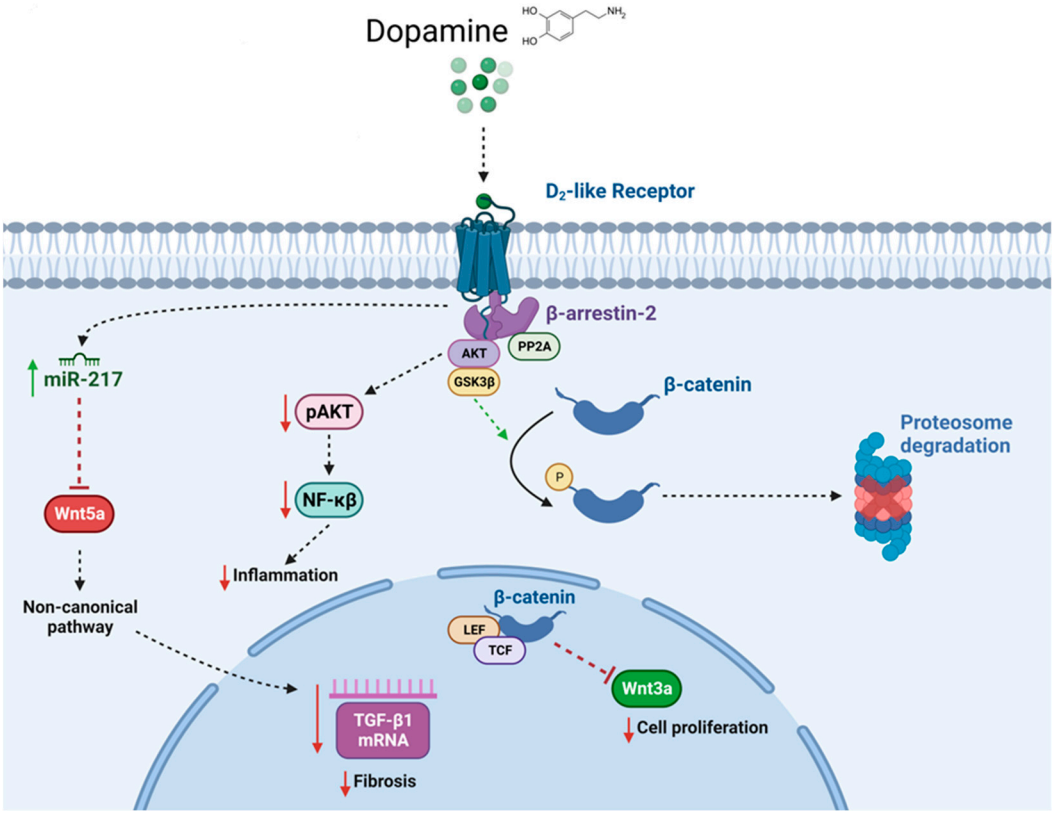

Figure 3. Pathways involved in the protective effect of D2R in the kidney. D2R stimulation, either by G-protein-dependent or G-protein-independent, β-arrestin-2- dependent pathways, increases the expression of miR-217, which downregulates the expression of Wnt5a and by a Wnt non-canonical pathway decreases the transcription of TGF-β1 and results in a decrease in fibrosis. The D2R β-arrestin-2-dependent pathway causes the recruitment of protein phosphatase 2 A (PP2A) and serine/threonine kinase AKT to the β-arrestin-2/D2R complex. PP2A dephosphorylates and inactivates AKT. AKT downregulates the expression of NF-kB and the transcription of a number of inflammatory factors. AKT also regulates through phosphorylation glycogen synthase kinase β (GSK3β), another key signaling kinase. In its non-phosphorylated state, GSK3β is constitutively active, whereas AKT-induced phosphorylation inactivates GSK3β and inhibits β-catenin-driven changes in gene expression, including Wnt3a, resulting in the regulation of cell proliferation.

The human *DRD2* gene is highly polymorphic. Several *DRD2* single nucleotide polymorphisms (SNPs), including rs6276 and rs6277, are associated not only with elevated blood pressure and hypertension but also with decreased D2R expression and thus function [169–173]. These polymorphisms are commonly observed with allele frequencies of 0.422 for rs6276 and 0.229 for rs6277 across several populations [174] In renal proximal tubule cells from subjects carrying rs6276 and rs6277 SNPs, the expression of D2R is decreased about 50% when compared with non-carriers [175,176]. In addition, a marked increase in pro-inflammatory and pro-fibrotic factors (inflammatory cytokines and chemokines, macrophage inflammatory protein-1β, NF-kB1A, IL-1F7, IL-10, IL-22, CCl24, and CXCL14) has been associated with the presence of these SNPs [168,175,176]. These cells also present a characteristic phenotype of epithelial—mesenchymal transition (EMT) with increased TGF-β signaling, a fibrotic pathway, and increased Smad3 and Snail1 transcription factors, resulting in increased collagen I, fibronectin 1, and vimentin synthesis [175]. Transient transfection of a plasmid harboring cDNA of human wild-type *DRD2* negated the pro-inflammatory and pro-fibrotic effects of the SNPs [175,176]. The increase in TGF-β1 is, in part, the result of the positive regulation of the D2R on the expression of miR-217. Cells carrying *DRD2* SNPs have a reduced expression of miR-217, which resulted in increased TGF-β1 by decreasing the miR-217 repressor effect on Wnt5a. Increased expression of Wnt5a and its receptor Ror2 increases the expression of TGF-β1 through the non-canonical Wnt pathway, resulting in EMT [176]. Moreover, reduced D2R expression in human renal proximal tubule cells is associated with increased Wnt3a expression, which then alters Wnt/β-catenin signaling and results in increased cell proliferation [168]. Importantly, SNPs in *DRD2* are associated with chronic kidney disease in Asian Indians with type-2 diabetes [177], which highlights the translational potential of understanding renal D2R signaling and its implications in health and disease.

2. Clinical Relevance

2.1. Genetics

Essential hypertension is a major consequence of chronic kidney disease (CKD). However, hypertension may cause progressive kidney disease only in genetically susceptible individuals [178–180]. Although genetic-linkage analyses and association studies [4,5,181,182] have implicated several loci and candidate genes in the predisposition to CKD, the genes that contribute to genetic susceptibility to this condition are largely unknown.

Kidney disease may result directly from gene mutations that lead to a dysfunctional protein. However, genetic factors may become evident only in the presence of systemic diseases, such as hypertension and diabetes mellitus, and affect the outcome of renal disease. The difference in the susceptibility to disease progression among patients may be explained by polymorphisms in genes that encode proteins, providing renal tissue protection from permanent damage. Identification of novel genetic factors that determine renal disease susceptibility may increase the understanding of the pathogenesis of CKD and the protective effects of endogenous molecules in the kidney may be exploited to counteract the growing incidence of CKD.

DRD2 SNPs that result in decreased expression are associated with susceptibility to diabetic nephropathy [177]. The analysis of 16 microarray studies deposited in GEO Datasets of CKD patients, controls, and transplanted kidneys with or without injury showed that in 13 out of the 16 studies, *DRD2* expression is lower in patients with CKD or transplanted kidneys with injury and deficient renal function than in patients with no CKD or transplanted kidneys with no evidence of injury (unpublished). Genetic testing can help to identify the individuals at risk and pharmacological treatment tailored to prevent or ameliorate the insult may decrease the prevalence of renal injury and CKD.

More than 90% of the *DRD2* SNPs are located in intronic and regulatory regions and can modify the interaction with miRNA, transcription factors, or ribosomal translation of mRNA [7]. Only a few polymorphisms are located in the coding region and may affect the protein function, structure, or stability; most of these SNPs are predicted to have

decreased protein stability and have pathologic effects [183]. Several of the *DRD2* SNPs are associated with a reduction in D2R expression. The frequency of rs1800497, (also known as Taq1 A, allele of the ANKK1 gene, previously reported to be located in the *DRD2*) is about 22% in the Caucasian population. This variation, which results in a 40% reduction in D2R expression in the striatum without affecting receptor affinity [170,171,184,185], is associated with a good weight loss response to naltrexone/bupropion [186]. This *DRD2* variant decreases D2R expression in human renal proximal tubule cells [175] and the Taq1A2A2 genotype is associated with hypertension with decreased iliac and tricep skinfold thickness [169,187–190] By contrast, the TaqA1 allele frequency is increased in individuals with type 2 diabetes [191].

DRD2 rs6277 has a frequency of about 50% in the Caucasian population. *DRD2* rs6277 is associated with decreased mRNA stability and translation, reduced DA-induced up-regulation of D2R membrane expression in vitro [172], and lower D2R expression in the cortex and striatum in healthy subjects [192–194]. *DRD2* rs6275 and *DRD2* rs6277 are associated with significant increases in blood glucose after controlling for BMI, age, sex, dosage, and type of antipsychotic medication in treated schizophrenics [195]. *DRD2* rs6276 and *DRD2* rs6277, which are also associated with a decrease renal D2R expression and function, may be important in the pathogenesis of inverse salt sensitivity, a state in which blood pressure is increased by a low salt diet. The presence of *DRD2* rs6276/rs6277 decreases the renal proximal tubule plasma membrane expression of D2R and its affinity to a D_2-like receptor antagonist. The decreased expression of D2R in cells expressing *DRD2* rs6276 can be related to the increased binding of miR-485-5p miRNA to the rs6276 sequence that represses D2R expression [196].

DRD2 rs6276, rs35608204, and rs1800499 are linked to and/or associated with type 2 diabetes and may be related to a repressed chromatin state in the endocrine pancreas, which is consistent with impaired insulin secretion and glucose intolerance [197]. rs1799732 (also known as −141 C Ins/Del) is located in the promoter region of the *DRD2*, with an allele frequency of about 9% in the Caucasian population [198]. This SNP is associated with decreased mRNA stability and translation, reducing the DA-induced up-regulation of D2R membrane expression in vitro [172]. *DRD2* rs2283265, rs1076560, and 1079727 alter mRNA splicing and transcription process in exon 6, leading to two isoforms of *DRD2*, which are D2 long and D2 short, and is associated with low mRNA expression levels [199–201]. More specifically, these SNPs were associated with reduced expression of the receptor in the prefrontal cortex and striatum in healthy subjects and in schizophrenics [202–204]. Two *DRD2* SNPs were associated with reductions in *DRD2* activity; rs1801028 is associated with reduced DA affinity [205] and rs1079597 with lower receptor binding [170]. By contrast, rs12364283 is associated with an increase in the D2R protein caused by an increase in mRNA expression levels [204,206]. The roles, if any, of these *DRD2* SNPs in blood pressure regulation and/or renal function are not known.

2.2. Effects of Antipsychotics on Systemic Inflammation

There is an increased mortality rate and shortened life expectancy in schizophrenic patients, among other reasons, because of the adverse effects of antipsychotic drugs, most of which are D2R antagonists or partial agonists [207,208]. The risk of acute and chronic kidney disease is increased in schizophrenic patients and also increases with the use of both typical and atypical antipsychotics [209,210]. Moreover, patients treated with several atypical antipsychotics have higher levels of cytokines and chemokines and are at higher risk of acute kidney injury than those treated with typical antipsychotics [211–213]. This is not a general finding, as the anti-inflammatory effect of an atypical antipsychotic has also been reported for risperidone with no anti-inflammatory effect of clozapine [214]. However, other studies have shown that clozapine increases the plasma levels of soluble tumor necrosis factors sTNFR1 and TNFR2, while haloperidol has no effects [212]. A population-based study in older adults also showed a greater risk of acute kidney injury in patients prescribed with atypical antipsychotic drugs than those not prescribed with

these drugs [215,216]. Furthermore, a meta-analysis of inflammatory biomarkers in healthy volunteers taking both typical and atypical antipsychotics had increased plasma levels of C-reactive protein, IL-6, and TNFα [217].

Schizophrenia, by itself, and treatment with clozapine or olanzapine are associated with weight gain, metabolic risk factors, morbidity, and modifications in cytokines and adipokines that are in part gender dependent [218,219]. Most studies have shown that in these patients, serum adiponectin levels are lower than in controls and are associated with the development of insulin resistance, metabolic syndrome, type 2 diabetes, and risk of cardiovascular events. Other atypical antipsychotics such as risperidone and paliperidone have an intermediate risk, while others such as aripiprazole have less or little effect on body weight. Similarly, typical antipsychotics also carry the potential risk of weight gain [220,221]. One of the potential mechanisms involved in the weight gain induced by antipsychotics is the blockade of D2R and D3R, as antipsychotic drugs that only interact with these receptors can significantly increase weight gain [222,223].

3. Conclusions

Dopamine is produced locally in several peripheral organs and different cell types and has autocrine and paracrine effects influencing many organ functions. Its negative effects on oxidative stress and inflammation involve several receptors, and the effects may be tissue- or organ-specific. In most tissues and several immune cells, D2-like receptors have anti-inflammatory and antifibrotic properties, while D1-like receptors anti-inflammatory effects are, for the most part, related to the regulation of oxidative stress and function of infiltrating immune cells. In the kidney, oxidative stress and inflammation are major mediators of the development and progression of disease. Low-grade inflammation is associated with cardiovascular disease. Infiltration of inflammatory cells and increased expression of proinflammatory factors are crucial in the development of renal injury, as well as in the induction and maintenance of hypertension. Human *DRD2* SNPs that decrease expression of the receptor are associated with hypertension and increase the susceptibility to chronic kidney disease. This is related to the loss of the antioxidant and anti-inflammatory effects of renal D2R. The implementation of genetic testing to identify individuals at risk and the tailoring of pharmacological treatment to ameliorate the insult should decrease the consequences of renal injury and, therefore, the prevalence of chronic kidney disease.

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References

1. Asghar, M.; Tayebati, S.K.; Lokhandwala, M.F.; Hussain, T. Potential Dopamine-1 Receptor Stimulation in Hypertension Management. *Curr. Hypertens. Rep.* **2011**, *13*, 294–302. [CrossRef]
2. Armando, I.; Villar, V.A.M.; Jose, P.A. Dopamine and Renal Function and Blood Pressure Regulation. *Compr. Physiol.* **2011**, *1*, 1075–1117. [CrossRef]
3. Bucolo, C.; Leggio, G.M.; Drago, F.; Salomone, S. Dopamine Outside the Brain: The Eye, Cardiovascular System and Endocrine Pancreas. *Pharmacol. Ther.* **2019**, *203*, 107392. [CrossRef] [PubMed]
4. Available online: https://www.ucsfhealth.org/medical-tests/catecholamine-blood-test#:~:text=Normal%20Results&text=The%20normal%20range%20for%20norepinephrine,to%2010048.7%20pmol%2FL (accessed on 7 March 2023).
5. Goldstein, D.S.; Swoboda, K.J.; Miles, J.M.; Coppack, S.W.; Aneman, A.; Holmes, C.; Lamensdorf, I.; Eisenhofer, G. Sources and Physiological Significance of Plasma Dopamine Sulfate. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 2523–2531. [CrossRef]
6. Miyajima, K.; Kawamoto, C.; Hara, S.; Mori-Kojima, M.; Ohye, T.; Sumi-Ichinose, C.; Saito, N.; Sasaoka, T.; Metzger, D.; Ichinose, H. Tyrosine Hydroxylase Conditional KO Mice Reveal Peripheral Tissue-Dependent Differences in Dopamine Biosynthetic Pathways. *J. Biol. Chem.* **2021**, *296*, 100544. [CrossRef] [PubMed]

7. Goldstein, D.S.; Mezey, E.; Yamamoto, T.; Aneman, A.; Friberg, P.; Eisenhofer, G. Is There a Third Peripheral Catecholaminergic System? Endogenous Dopamine as an Autocrine/Paracrine Substance Derived from Plasma DOPA and Inactivated by Conjugation. *Hypertens. Res.* **1995**, *18* (Suppl. S1), S93–S99. [CrossRef] [PubMed]
8. Feng, Y.; Lu, Y. Immunomodulatory Effects of Dopamine in Inflammatory Diseases. *Front. Immunol.* **2021**, *12*, 663102. [CrossRef] [PubMed]
9. McKenna, F.; McLaughlin, P.J.; Lewis, B.J.; Sibbring, G.C.; Cummerson, J.A.; Bowen-Jones, D.; Moots, R.J. Dopamine Receptor Expression on Human T- and B-Lymphocytes, Monocytes, Neutrophils, Eosinophils and NK Cells: A Flow Cytometric Study. *J. Neuroimmunol.* **2002**, *132*, 34–40. [CrossRef] [PubMed]
10. Sarkar, C.; Basu, B.; Chakroborty, D.; Dasgupta, P.S.; Basu, S. The immunoregulatory role of dopamine: An update. *Brain Behav. Immun.* **2010**, *24*, 525–528. [CrossRef]
11. Shao, W.; Zhang, S.; Tang, M.; Zhang, X.; Zhou, Z.; Yin, Y.; Zhou, Q.; Huang, Y.; Liu, Y.; Wawrousek, E.; et al. Suppression of Neuroinflammation by Astrocytic Dopamine D2 Receptors via AB-Crystallin. *Nature* **2013**, *494*, 90–94. [CrossRef]
12. Torres-Rosas, R.; Yehia, G.; Peña, G.; Mishra, P.; del Rocio Thompson-Bonilla, M.; Moreno-Eutimio, M.A.; Arriaga-Pizano, L.A.; Isibasi, A.; Ulloa, L. Dopamine Mediates Vagal Modulation of the Immune System by Electroacupuncture. *Nat. Med.* **2014**, *20*, 291–295. [CrossRef]
13. Yan, Y.; Jiang, W.; Liu, L.; Wang, X.; Ding, C.; Tian, Z.; Zhou, R. Dopamine Controls Systemic Inflammation through Inhibition of NLRP3 Inflammasome. *Cell* **2015**, *160*, 62–73. [CrossRef] [PubMed]
14. Levite, M. Dopamine and T Cells: Dopamine Receptors and Potent Effects on T Cells, Dopamine Production in T Cells, and Abnormalities in the Dopaminergic System in T Cells in Autoimmune, Neurological and Psychiatric Diseases. *Acta Physiol.* **2016**, *216*, 42–89. [CrossRef]
15. Brito-Melo, G.E.A.; Nicolato, R.; de Oliveira, A.C.P.; Menezes, G.B.; Lélis, F.J.N.; Avelar, R.S.; Sá, J.; Bauer, M.E.; Souza, B.R.; Teixeira, A.L.; et al. Increase in Dopaminergic, but Not Serotoninergic, Receptors in T-Cells as a Marker for Schizophrenia Severity. *J. Psychiatr. Res.* **2012**, *46*, 738–742. [CrossRef] [PubMed]
16. Prado, C.; Contreras, F.; González, H.; Díaz, P.; Elgueta, D.; Barrientos, M.; Herrada, A.A.; Lladser, Á.; Bernales, S.; Pacheco, R. Stimulation of Dopamine Receptor D5 Expressed on Dendritic Cells Potentiates Th17-Mediated Immunity. *J. Immunol.* **2012**, *188*, 3062–3070. [CrossRef] [PubMed]
17. Marino, F.; Pinoli, M.; Rasini, E.; Martini, S.; Luini, A.; Pulze, L.; Dalla Gasperina, D.; Grossi, P.; Legnaro, M.; Ferrari, M.; et al. Dopaminergic Inhibition of Human Neutrophils Is Exerted through D1-like Receptors and Affected by Bacterial Infection. *Immunology* **2022**, *167*, 508–527. [CrossRef]
18. Mori, T.; Kabashima, K.; Fukamachi, S.; Kuroda, E.; Sakabe, J.; Kobayashi, M.; Nakajima, S.; Nakano, K.; Tanaka, Y.; Matsushita, S.; et al. D1-like Dopamine Receptors Antagonist Inhibits Cutaneous Immune Reactions Mediated by Th2 and Mast Cells. *J. Dermatol. Sci.* **2013**, *71*, 37–44. [CrossRef]
19. Kustrimovic, N.; Rasini, E.; Legnaro, M.; Marino, F.; Cosentino, M. Expression of Dopaminergic Receptors on Human CD4+ T Lymphocytes: Flow Cytometric Analysis ofIe and Memory Subsets and Relevance for the Neuroimmunology of Neurodegenerative Disease. *J. Neuroimmune Pharmacol.* **2014**, *9*, 302–312. [CrossRef]
20. Pacheco, R.; Contreras, F.; Zouali, M. The Dopaminergic System in Autoimmune Diseases. *Front. Immunol.* **2014**, *5*, 117. [CrossRef]
21. González, H.; Contreras, F.; Prado, C.; Elgueta, D.; Franz, D.; Bernales, S.; Pacheco, R. Dopamine Receptor D3 Expressed on CD4+ T Cells Favors Neurodegeneration of Dopaminergic Neurons during Parkinson's Disease. *J. Immunol.* **2013**, *190*, 5048–5056. [CrossRef]
22. Bach, F.; Grundmann, U.; Bauer, M.; Buchinger, H.; Soltész, S.; Graeter, T.; Larsen, R.; Silomon, M. Modulation of the Inflammatory Response to Cardiopulmonary Bypass by Dopexamine and Epidural Anesthesia. *Acta Anaesthesiol. Scand.* **2002**, *46*, 1227–1235. [CrossRef] [PubMed]
23. Birnbaum, J.; Klotz, E.; Spies, C.D.; Lorenz, B.; Stuebs, P.; Hein, O.V.; Grundling, M.; Pavlovic, D.; Usichenko, T.; Wendt, M.; et al. Effects of Dopexamine on the Intestinal Microvascular Blood Flow and Leukocyte Activation in a Sepsis Model in Rats. *Crit. Care* **2006**, *10*, R117. [CrossRef]
24. Ghosh, M.C.; Mondal, A.C.; Basu, S.; Banerjee, S.; Majumder, J.; Bhattacharya, D.; Dasgupta, P.S. Dopamine Inhibits Cytokine Release and Expression of Tyrosine Kinases, Lck and Fyn in Activated T Cells. *Int. Immunopharmacol.* **2003**, *3*, 1019–1026. [CrossRef]
25. Nakano, K.; Higashi, T.; Hashimoto, K.; Takagi, R.; Tanaka, Y.; Matsushita, S. Antagonizing Dopamine D1-like Receptor Inhibits Th17 Cell Differentiation: Preventive and Therapeutic Effects on Experimental Autoimmune Encephalomyelitis. *Biochem. Biophys. Res. Commun.* **2008**, *373*, 286–291. [CrossRef] [PubMed]
26. Hashimoto, K.; Inoue, T.; Higashi, T.; Takei, S.-I.; Awata, T.; Katayama, S.; Takagi, R.; Okada, H.; Matsushita, S. Dopamine D1-like Receptor Antagonist, SCH23390, Exhibits a Preventive Effect on Diabetes Mellitus That Occurs Naturally in NOD Mice. *Biochem. Biophys. Res. Commun.* **2009**, *383*, 460–463. [CrossRef] [PubMed]
27. Okada, H.; Inoue, T.; Hashimoto, K.; Suzuki, H.; Matsushita, S. D1-like receptor antagonist inhibits IL-17 expression and attenuates crescent formation in nephrotoxic serum nephritis. *Am. J. Nephrol.* **2009**, *30*, 274–279. [CrossRef]
28. Haskó, G.; Szabó, C.; Németh, Z.H.; Deitch, E.A. Dopamine Suppresses IL-12 P40 Production by Lipopolysaccharide-Stimulated Macrophages via a Beta-Adrenoceptor-Mediated Mechanism. *J. Neuroimmunol.* **2002**, *122*, 34–39. [CrossRef]

29. Liu, A.; Ding, S. Anti-Inflammatory Effects of Dopamine in Lipopolysaccharide (LPS)-Stimulated RAW264.7 Cells via Inhibiting NLRP3 Inflammasome Activation. *Ann. Clin. Lab. Sci.* **2019**, *49*, 353–360.
30. Sadeghi, H.; Parishani, M.; Akbartabar Touri, M.; Ghavamzadeh, M.; Jafari Barmak, M.; Zarezade, V.; Delaviz, H.; Sadeghi, H. Pramipexole reduces inflammation in the experimental animal models of inflammation. *Immunopharmacol. Immunotoxicol.* **2017**, *39*, 80–86. [CrossRef]
31. Bendele, A.M.; Spaethe, S.M.; Benslay, D.N.; Bryant, H.U. Anti-Inflammatory Activity of Pergolide, a Dopamine Receptor Agonist. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 169–175.
32. Huang, Y.; Chen, C.-C.; Wang, T.-T.; Qiu, Y.-H.; Peng, Y.-P. Dopamine Receptors Modulate T Lymphocytes via Inhibition of CAMP-CREB Signaling Pathway. *Neuro Endocrinol. Lett.* **2016**, *37*, 491–500.
33. Han, X.; Ni, J.; Wu, Z.; Wu, J.; Li, B.; Ye, X.; Dai, J.; Chen, C.; Xue, J.; Wan, R.; et al. Myeloid-Specific Dopamine D2 Receptor Signalling Controls Inflammation in Acute Pancreatitis via Inhibiting M1 Macrophage. *Br. J. Pharmacol.* **2020**, *177*, 2991–3008. [CrossRef]
34. Yamamoto, S.; Ohta, N.; Matsumoto, A.; Horiguchi, Y.; Koide, M.; Fujino, Y. Haloperidol Suppresses NF-KappaB to Inhibit Lipopolysaccharide-Induced Pro-Inflammatory Response in RAW 264 Cells. *Med. Sci. Monit.* **2016**, *22*, 367–372. [CrossRef] [PubMed]
35. Schetz, J.A.; Benjamin, P.S.; Sibley, D.R. Nonconserved residues in the second transmembrane-spanning domain of the D(4) dopamine receptor are molecular determinants of D(4)-selective pharmacology. *Mol. Pharmacol.* **2000**, *57*, 144–152.
36. Anlauf, M.; Schäfer, M.K.-H.; Eiden, L.; Weihe, E. Chemical Coding of the Human Gastrointestinal Nervous System: Cholinergic, VIPergic, and Catecholaminergic Phenotypes. *J. Comp. Neurol.* **2003**, *459*, 90–111. [CrossRef] [PubMed]
37. Li, Z.S.; Pham, T.D.; Tamir, H.; Chen, J.J.; Gershon, M.D. Enteric Dopaminergic Neurons: Definition, Developmental Lineage, and Effects of Extrinsic Denervation. *J. Neurosci.* **2004**, *24*, 1330–1339. [CrossRef]
38. Vieira-Coelho, M.A.; Soares-da-Silva, P. Dopamine Formation, from Its Immediate Precursor 3,4-Dihydroxyphenylalanine, along the Rat Digestive Tract. *Fundam. Clin. Pharmacol.* **1993**, *7*, 235–243. [CrossRef] [PubMed]
39. Li, M.; Zhang, C.; Zhou, L.; Wang, T.; Fu, F. Continuous Activation of Dopamine Receptors Alleviates LPS-Induced Liver Injury in Mice via β-arrestin2 Dependent Akt/NF-κB Pathway. *Front. Pharmacol.* **2022**, *13*, 853834. [CrossRef]
40. Herak-Perković, V.; Grabarević, Z.; Banić, M.; Anić, B.; Novosel, V.; Pogacnik, M. Effects of Dopaminergic Drugs on Inflammatory Bowel Disease Induced with 2,4-Dinitrofluorbenzene in BALB/c Mice. *J. Vet. Pharmacol. Ther.* **2001**, *24*, 267–273. [CrossRef]
41. Ugalde, V.; Contreras, F.; Prado, C.; Chovar, O.; Espinoza, A.; Pacheco, R. Dopaminergic Signalling Limits Suppressive Activity and Gut Homing of Regulatory T Cells upon Intestinal Inflammation. *Mucosal Immunol.* **2021**, *14*, 652–666. [CrossRef]
42. Magro, F.; Vieira-Coelho, M.A.; Fraga, S.; Serrão, M.P.; Veloso, F.T.; Ribeiro, T.; Soares-da-Silva, P. Impaired Synthesis or Cellular Storage of Norepinephrine, Dopamine, and 5-Hydroxytryptamine in Human Inflammatory Bowel Disease. *Dig. Dis. Sci.* **2002**, *47*, 216–224. [CrossRef] [PubMed]
43. Tolstanova, G.; Deng, X.; Ahluwalia, A.; Paunovic, B.; Prysiazhniuk, A.; Ostapchenko, L.; Tarnawski, A.; Sandor, Z.; Szabo, S. Role of Dopamine and D2 Dopamine Receptor in the Pathogenesis of Inflammatory Bowel Disease. *Dig. Dis. Sci.* **2015**, *60*, 2963–2975. [CrossRef] [PubMed]
44. Aslanoglou, D.; Bertera, S.; Friggeri, L.; Sánchez-Soto, M.; Lee, J.; Xue, X.; Logan, R.W.; Lane, J.R.; Yechoor, V.K.; McCormick, P.J.; et al. Dual Pancreatic Adrenergic and Dopaminergic Signaling as a Therapeutic Target of Bromocriptine. *iScience* **2022**, *25*, 104771. [CrossRef] [PubMed]
45. Li, G.-W.; Li, J.; Feng, X.-Y.; Chen, H.; Chen, Y.; Liu, J.-H.; Zhang, Y.; Hong, F.; Zhu, J.-X. Pancreatic Acinar Cells Utilize Tyrosine to Synthesize L-Dihydroxyphenylalanine. *Exp. Biol. Med.* **2021**, *246*, 2533–2542. [CrossRef]
46. Rubí, B.; Ljubicic, S.; Pournourmohammadi, S.; Carobbio, S.; Armanet, M.; Bartley, C.; Maechler, P. Dopamine D2-like Receptors Are Expressed in Pancreatic Beta Cells and Mediate Inhibition of Insulin Secretion. *J. Biol. Chem.* **2005**, *280*, 36824–36832. [CrossRef]
47. Farino, Z.J.; Morgenstern, T.J.; Maffei, A.; Quick, M.; De Solis, A.J.; Wiriyasermkul, P.; Freyberg, R.J.; Aslanoglou, D.; Sorisio, D.; Inbar, B.P.; et al. New Roles for Dopamine D2 and D3 Receptors in Pancreatic Beta Cell Insulin Secretion. *Mol. Psychiatry* **2020**, *25*, 2070–2085. [CrossRef]
48. Mezey, E.; Eisenhofer, G.; Harta, G.; Hansson, S.; Gould, L.; Hunyady, B.; Hoffman, B.J. A Novel Nonneuronal Catecholaminergic System: Exocrine Pancreas Synthesizes and Releases Dopamine. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 10377–10382. [CrossRef]
49. Karanjia, N.D.; Widdison, A.L.; Lutrin, F.J.; Chang, Y.-B.; Reber, H.A. The Antiinflammatory Effect of Dopamine in Alcoholic Hemorrhagic Pancreatitis in Cats: Studies on the Receptors and Mechanisms of Action. *Gastroenterology* **1991**, *101*, 1635–1641. [CrossRef]
50. Han, X.; Li, B.; Ye, X.; Mulatibieke, T.; Wu, J.; Dai, J.; Wu, D.; Ni, J.; Zhang, R.; Xue, J.; et al. Dopamine D2 Receptor Signalling Controls Inflammation in Acute Pancreatitis via a PP2A-Dependent Akt/NF-KB Signalling Pathway. *Br. J. Pharmacol.* **2017**, *174*, 4751–4770. [CrossRef]
51. Ye, X.; Han, X.; Li, B.; Dai, J.; Wu, Z.; He, Y.; Wen, L.; Hu, G. Dopamine D2 Receptor Activator Quinpirole Protects against Trypsinogen Activation during Acute Pancreatitis via Upregulating HSP70. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2020**, *318*, G1000–G1012. [CrossRef]
52. Mignini, F.; Tomassoni, D.; Traini, E.; Amenta, F. Dopamine, Vesicular Transporters and Dopamine Receptor Expression and Localization in Rat Thymus and Spleen. *J. Neuroimmunol.* **2009**, *206*, 5–13. [CrossRef] [PubMed]

53. Carr, L.; Tucker, A.; Fernandez-Botran, R. In Vivo Administration of L-Dopa or Dopamine Decreases the Number of Splenic IFN Gamma-Producing Cells. *J. Neuroimmunol.* **2003**, *137*, 87–93. [CrossRef] [PubMed]
54. Zhao, W.; Huang, Y.; Liu, Z.; Cao, B.-B.; Peng, Y.-P.; Qiu, Y.-H. Dopamine Receptors Modulate Cytotoxicity of Natural Killer Cells via CAMP-PKA-CREB Signaling Pathway. *PLoS ONE* **2013**, *8*, e65860. [CrossRef]
55. Feketeova, E.; Li, Z.; Joseph, B.; Shah, R.; Spolarics, Z.; Ulloa, L. Dopaminergic Control of Inflammation and Glycemia in Sepsis and Diabetes. *Front. Immunol.* **2018**, *9*, 943. [CrossRef] [PubMed]
56. Yue, S.; Wang, T.; Yang, Y.; Fan, Y.; Zhou, L.; Li, M.; Fu, F. Lipopolysaccharide/D-galactosamine-induced acute liver injury could be attenuated by dopamine receptor agonist rotigotine via regulating NF-κB signaling pathway. *Int. Immunopharmacol.* **2021**, *96*, 107798. [CrossRef] [PubMed]
57. Zhou, H.; Tang, L.; Yang, Y.; Lin, L.; Dai, J.; Pu, G.; Ai, Q.; Jiang, R.; Zhang, L. Dopamine Alleviated Acute Liver Injury Induced by Lipopolysaccharide/d-Galactosamine in Mice. *Int. Immunopharmacol.* **2018**, *61*, 249–255. [CrossRef]
58. Peng, X.; Yang, Y.; Tang, L.; Wan, J.; Dai, J.; Li, L.; Huang, J.; Shen, Y.; Lin, L.; Gong, X.; et al. Therapeutic benefits of apocynin in mice with lipopolysaccharide/D-galactosamine-induced acute liver injury via suppression of the late stage pro-apoptotic AMPK/JNK pathway. *Biomed. Pharmacother.* **2020**, *125*, 110020. [CrossRef]
59. Yang, C.; He, L.; Wang, C.; Huang, Y.; Wang, A.; Li, X.; Ao, J. Dexmedetomidine alleviated lipopolysaccharide/D-galactosamine-induced acute liver injury in mice. *Int. Immunopharmacol.* **2019**, *72*, 367–373. [CrossRef]
60. Xue, R.; Zhang, H.; Pan, J.; Du, Z.; Zhou, W.; Zhang, Z.; Tian, Z.; Zhou, R.; Bai, L. Peripheral Dopamine Controlled by Gut Microbes Inhibits Invariant Natural Killer T Cell-Mediated Hepatitis. *Front. Immunol.* **2018**, *9*, 2398. [CrossRef]
61. Liu, X.-F.; Long, H.-J.; Miao, X.-Y.; Liu, G.-L.; Yao, H.-L. Fisetin Inhibits Liver Cancer Growth in a Mouse Model: Relation to Dopamine Receptor. *Oncol. Rep.* **2017**, *38*, 53–62. [CrossRef]
62. Harkitis, P.; Daskalopoulos, E.P.; Malliou, F.; Lang, M.A.; Marselos, M.; Fotopoulos, A.; Albucharali, G.; Konstandi, M. Dopamine D2-Receptor Antagonists Down-Regulate CYP1A1/2 and CYP1B1 in the Rat Liver. *PLoS ONE* **2015**, *10*, e0128708. [CrossRef]
63. Aviado, D.M.; Sadavongvivad, C. Pharmacological Significance of Biogenic Amines in the Lungs: Noradrenaline and Dopamine. *Br. J. Pharmacol.* **1970**, *38*, 374–385. [CrossRef] [PubMed]
64. Adir, Y.; Azzam, Z.S.; Lecuona, E.; Leal, S.; Pesce, L.; Dumasius, V.; Bertorello, A.M.; Factor, P.; Young, J.B.; Ridge, K.M.; et al. Augmentation of Endogenous Dopamine Production Increases Lung Liquid Clearance. *Am. J. Respir. Crit. Care Med.* **2004**, *169*, 757–763. [CrossRef] [PubMed]
65. Kim, M.O.; Koh, P.O.; Kim, J.H.; Kim, J.S.; Kang, S.S.; Cho, G.J.; Kim, K.; Choi, W.S. Localization of Dopamine D1 and D2 Receptor mRNAs in the Rat Systemic and Pulmonary Vasculatures. *Mol. Cells* **1999**, *9*, 417–421. [PubMed]
66. Kobayashi, Y.; Ricci, A.; Amenta, F. Autoradiographic Localization of Dopamine D1-like Receptors in the Rabbit Pulmonary Circulation. *Eur. J. Pharmacol.* **1994**, *253*, 201–206. [CrossRef] [PubMed]
67. Kobayashi, Y.; Cavallotti, D.; Ricci, A.; Amenta, F. Localisation of Dopamine D2-like Receptors in Pulmonary Artery of the Human and Rabbit but Not of the Rat. *Eur. J. Pharmacol.* **1994**, *261*, 229–236. [CrossRef] [PubMed]
68. Bairam, A.; Frenette, J.; Dauphin, C.; Carroll, J.L.; Khandjian, E.W. Expression of Dopamine D1-Receptor MRNA in the Carotid Body of Adult Rabbits, Cats and Rats. *Neurosci. Res.* **1998**, *31*, 147–154. [CrossRef]
69. Bairam, A.; Néji, H.; De-Grandpré, P.; Carroll, J.L. Autoreceptor Mechanism Regulating Carotid Body Dopamine Release from Adult and 10-Day-Old Rabbits. *Respir. Physiol.* **2000**, *120*, 27–34. [CrossRef]
70. Ciarka, A.; Vincent, J.-L.; van de Borne, P. The Effects of Dopamine on the Respiratory System: Friend or Foe? *Pulm. Pharmacol. Ther.* **2007**, *20*, 607–615. [CrossRef]
71. Peiser, C.; Trevisani, M.; Groneberg, D.A.; Dinh, Q.T.; Lencer, D.; Amadesi, S.; Maggiore, B.; Harrison, S.; Geppetti, P.; Fischer, A. Dopamine Type 2 Receptor Expression and Function in Rodent Sensory Neurons Projecting to the Airways. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2005**, *289*, L153–L158. [CrossRef]
72. Alan, P.N.D.M.J.; Ince, Y.I.G.D.F.; Holt, K.M.R.P.R. Dual D2 Dopamine Receptor and SS2-Adrenoceptor Agonists for the Modulation of Sensory Nerves in COPD. *New Drugs Asthma Allergy COPD* **2001**, *31*, 68–71.
73. Bone, N.B.; Liu, Z.; Pittet, J.-F.; Zmijewski, J.W. Frontline Science: D1 Dopaminergic Receptor Signaling Activates the AMPK-Bioenergetic Pathway in Macrophages and Alveolar Epithelial Cells and Reduces Endotoxin-Induced ALI. *J. Leukoc. Biol.* **2017**, *101*, 357–365. [CrossRef] [PubMed]
74. Matsuyama, N.; Shibata, S.; Matoba, A.; Kudo, T.-A.; Danielsson, J.; Kohjitani, A.; Masaki, E.; Emala, C.W.; Mizuta, K. The Dopamine D1 Receptor Is Expressed and Induces CREB Phosphorylation and MUC5AC Expression in Human Airway Epithelium. *Respir. Res.* **2018**, *19*, 53. [CrossRef] [PubMed]
75. Vohra, P.K.; Hoeppner, L.H.; Sagar, G.; Dutta, S.K.; Misra, S.; Hubmayr, R.D.; Mukhopadhyay, D. Dopamine Inhibits Pulmonary Edema through the VEGF-VEGFR2 Axis in a Murine Model of Acute Lung Injury. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2012**, *302*, L185–L192. [CrossRef]
76. Tonnarini, G.; Parlapiano, C.; Cavallotti, D.; Tego, A.; Curione, M.; Giancaspro, G.; Vincentelli, G.M.; Leone, S.; Cavallotti, C. Dopamine Receptor Subtypes in the Human Coronary Vessels of Healthy Subjects. *J. Recept. Signal Transduct. Res.* **2011**, *31*, 33–38. [CrossRef]
77. Cavallotti, C.; Mancone, M.; Bruzzone, P.; Sabbatini, M.; Mignini, F. Dopamine Receptor Subtypes in the Native Human Heart. *Heart Vessels* **2010**, *25*, 432–437. [CrossRef]

78. Liu, J.; Jin, Y.; Wang, B.; Wang, Y.; Zuo, S.; Zhang, J. Dopamine D1 receptor alleviates doxorubicin-induced cardiac injury by inhibiting NLRP3 inflammasome. *Biochem. Biophys. Res. Commun.* **2021**, *561*, 7–13. [CrossRef]
79. Li, H.; Shi, S.; Sun, Y.-H.; Zhao, Y.-J.; Li, Q.-F.; Li, H.-Z.; Wang, R.; Xu, C.-Q. Dopamine D2 Receptor Stimulation Inhibits Angiotensin II-Induced Hypertrophy in Cultured Neonatal Rat Ventricular Myocytes. *Clin. Exp. Pharmacol. Physiol.* **2009**, *36*, 312–318. [CrossRef]
80. Li, H.; Guo, J.; Gao, J.; Han, L.; Jiang, C.; Li, H.; Bai, S.; Zhang, W.; Li, G.; Wang, L.; et al. Role of Dopamine D2 Receptors in Ischemia/Reperfusion Induced Apoptosis of Cultured Neonatal Rat Cardiomyocytes. *J. Biomed. Sci.* **2011**, *18*, 18. [CrossRef]
81. Aguayo-Cerón, K.A.; Calzada-Mendoza, C.C.; Méndez-Bolaina, E.; Romero-Nava, R.; Ocharan-Hernández, M.E. The Regulatory Effect of Bromocriptine on Cardiac Hypertrophy by Prolactin and D2 Receptor Modulation. *Clin. Exp. Hypertens.* **2020**, *42*, 675–679. [CrossRef]
82. Gupta, V.; Goyal, R.; Sharma, P.L. Preconditioning Offers Cardioprotection in Hyperlipidemic Rat Hearts: Possible Role of Dopamine (D2) Signaling. *BMC Cardiovasc. Disord.* **2015**, *15*, 77. [CrossRef] [PubMed]
83. Yan, H.; Li, W.-L.; Xu, J.-J.; Zhu, S.-Q.; Long, X.; Che, J.-P. D2 Dopamine Receptor Antagonist Raclopride Induces Non-Canonical Autophagy in Cardiac Myocytes. *J. Cell Biochem.* **2013**, *114*, 103–110. [CrossRef]
84. Li, H.; Wei, C.; Gao, J.; Bai, S.; Li, H.; Zhao, Y.; Li, H.; Han, L.; Tian, Y.; Yang, G.; et al. Mediation of Dopamine D2 Receptors Activation in Post-Conditioning-Attenuated Cardiomyocyte Apoptosis. *Exp. Cell Res.* **2014**, *323*, 118–130. [CrossRef] [PubMed]
85. Gao, J.; Guo, J.; Li, H.; Bai, S.; Li, H.; Wu, B.; Wang, L.; Xi, Y.; Tian, Y.; Yang, G.; et al. Involvement of Dopamine D2 Receptors Activation in Ischemic Post-Conditioning-Induced Cardioprotection through Promoting PKC-ε Particulate Translocation in Isolated Rat Hearts. *Mol. Cell Biochem.* **2013**, *379*, 267–276. [CrossRef] [PubMed]
86. Gaweda, G.; Iyer, R.P.; Shaver, P.R.; Grilo, G.A.; Dinkins, M.-L.; Stoffel, H.J.; Clemens, S.; de Castro Brás, L.E. Dopamine Receptor D3 Agonist (Pramipexole) Reduces Morphine-Induced Cardiac Fibrosis. *Biochem. Biophys. Res. Commun.* **2020**, *529*, 1080–1085. [CrossRef]
87. Johnson, T.L.; Tulis, D.A.; Keeler, B.E.; Virag, J.A.; Lust, R.M.; Clemens, S. The Dopamine D3 Receptor Knockout Mouse Mimics Aging-Related Changes in Autonomic Function and Cardiac Fibrosis. *PLoS ONE* **2013**, *8*, e74116. [CrossRef]
88. Liu, X.-S.; Zeng, J.; Yang, Y.-X.; Qi, C.-L.; Xiong, T.; Wu, G.-Z.; Zeng, C.-Y.; Wang, D.-X. DRD4 Mitigates Myocardial Ischemia/Reperfusion Injury in Association With PI3K/AKT Mediated Glucose Metabolism. *Front. Pharmacol.* **2020**, *11*, 619426. [CrossRef]
89. Niewiarowska-Sendo, A.; Kozik, A.; Guevara-Lora, I. Influence of Bradykinin B2 Receptor and Dopamine D2 Receptor on the Oxidative Stress, Inflammatory Response, and Apoptotic Process in Human Endothelial Cells. *PLoS ONE* **2018**, *13*, e0206443. [CrossRef]
90. Kang, H.; Yu, H.; Fan, J.; Cao, G. Rotigotine Protects against Oxidized Low-Density Lipoprotein(Ox-LDL)-Induced Damages in Human Umbilical Vein Endothelial Cells(HUVECs). *Bioengineered* **2021**, *12*, 10568–10579. [CrossRef]
91. Sookhai, S.; Wang, J.H.; Winter, D.; Power, C.; Kirwan, W.; Redmond, H.P. Dopamine Attenuates the Chemoattractant Effect of Interleukin-8: A Novel Role in the Systemic Inflammatory Response Syndrome. *Shock* **2000**, *14*, 295–299. [CrossRef]
92. Kapper, S.; Beck, G.; Riedel, S.; Prem, K.; Haak, M.; van der Woude, F.J.; Yard, B.A. Modulation of chemokine production and expression of adhesion molecules in renal tubular epithelial and endothelial cells by catecholamines. *Transplantation* **2002**, *74*, 253–260. [CrossRef] [PubMed]
93. Borcherding, D.C.; Hugo, E.R.; Idelman, G.; De Silva, A.; Richtand, N.W.; Loftus, J.; Ben-Jonathan, N. Dopamine Receptors in Human Adipocytes: Expression and Functions. *PLoS ONE* **2011**, *6*, e25537. [CrossRef] [PubMed]
94. Leite, F.; Ribeiro, L. Dopaminergic Pathways in Obesity-Associated Inflammation. *J. Neuroimmune Pharmacol.* **2020**, *15*, 93–113. [CrossRef] [PubMed]
95. Wang, X.; Villar, V.A.; Tiu, A.; Upadhyay, K.K.; Cuevas, S. Dopamine D2 Receptor Upregulates Leptin and IL-6 in Adipocytes. *J. Lipid Res.* **2018**, *59*, 607–614. [CrossRef] [PubMed]
96. Kohlie, R.; Perwitz, N.; Resch, J.; Schmid, S.M.; Lehnert, H.; Klein, J.; Iwen, K.A. Dopamine Directly Increases Mitochondrial Mass and Thermogenesis in Brown Adipocytes. *J. Mol. Endocrinol.* **2017**, *58*, 57–66. [CrossRef]
97. Raffaelli, F.-M.; Resch, J.; Oelkrug, R.; Iwen, K.A.; Mittag, J. Dopamine Receptor D1- and D2-Agonists Do Not Spark Brown Adipose Tissue Thermogenesis in Mice. *Sci. Rep.* **2020**, *10*, 20203. [CrossRef]
98. Zeng, C.; Zhang, M.; Asico, L.D.; Eisner, G.M.; Jose, P.A. The Dopaminergic System in Hypertension. *Clin. Sci.* **2007**, *112*, 583–597. [CrossRef]
99. Yang, H.; Xu, Y.; Zhu, M.; Gu, Y.; Zhang, W.; Shao, H.; Wang, Y.; Ping, Z.; Hu, X.; Wang, L.; et al. Inhibition of Titanium-Particle-Induced Inflammatory Osteolysis after Local Administration of Dopamine and Suppression of Osteoclastogenesis via D2-like Receptor Signaling Pathway. *Biomaterials* **2016**, *80*, 1–10. [CrossRef]
100. Lu, J.-H.; Liu, Y.-Q.; Deng, Q.-W.; Peng, Y.-P.; Qiu, Y.-H. Dopamine D2 Receptor Is Involved in Alleviation of Type II Collagen-Induced Arthritis in Mice. *Biomed. Res. Int.* **2015**, *2015*, 496759. [CrossRef]
101. Puyó, A.M.; Levin, G.M.; Armando, I.; Barontini, M.B. Free and Conjugated Plasma Catecholamines in Pheochromocytoma Patients with and without Sustained Hypertension. *Acta Endocrinol.* **1986**, *113*, 111–117. [CrossRef]
102. Da Prada, M.; Zürcher, M. Simultaneous Radioenzymatic Determination of Plasma and Tissue Adrenaline, Noradrenaline and Dopamine within the Femtomole Range. *Life Sci.* **1976**, *19*, 1161–1174. [CrossRef]

103. Baines, A.D. Effects of Salt Intake and Renal Denervation on Catecholamine Catabolism and Excretion. *Kidney Int.* **1982**, *21*, 316–322. [CrossRef] [PubMed]
104. Goldstein, D.S.; Grossman, E.; Armando, I.; Wolfovitz, E.; Folio, C.J.; Holmes, C.; Keiser, H.R. Correlates of Urinary Excretion of Catechols in Humans. *Biog. Amines* **1993**, *10*, 3–17.
105. Lee, M.R. Dopamine and the Kidney: Ten Years On. *Clin. Sci.* **1993**, *84*, 357–375. [CrossRef]
106. Wang, Z.Q.; Siragy, H.M.; Felder, R.A.; Carey, R.M. Intrarenal Dopamine Production and Distribution in the Rat. Physiological Control of Sodium Excretion. *Hypertension* **1997**, *29*, 228–234. [CrossRef]
107. Bell, C. Dopamine Release from Sympathetic Nerve Terminals. *Prog. Neurobiol.* **1988**, *30*, 193–208. [CrossRef]
108. Dinerstein, R.J.; Vannice, J.; Henderson, R.C.; Roth, L.J.; Goldberg, L.I.; Hoffmann, P.C. Histofluorescence Techniques Provide Evidence for Dopamine-Containing Neuronal Elements in Canine Kidney. *Science* **1979**, *205*, 497–499. [CrossRef] [PubMed]
109. Adam, W.R.; Adams, B.A. Production and Excretion of Dopamine by the Isolated Perfused Rat Kidney. *Ren. Physiol.* **1985**, *8*, 150–158. [CrossRef] [PubMed]
110. Akama, H.; Noshiro, T.; Sano, N.; Watanabe, T.; Trigg, L.; Kotsonis, P.; Majewski, H.; McGrath, B.P.; Miura, Y.; Abe, K. Effects of Isotonic Saline Loading on Renal Tubular and Neurogenic Dopamine Release in Conscious Rabbits. *Clin. Exp. Pharmacol. Physiol.* **1995**, *22*, 469–471. [CrossRef]
111. Berndt, T.J.; Khraibi, A.A.; Thothathri, V.; Dousa, T.P.; Tyce, G.M.; Knox, F.G. Effect of Increased Dietary Phosphate Intake on Dopamine Excretion in the Presence and Absence of the Renal Nerves. *Miner. Electrolyte Metab.* **1994**, *20*, 158–162. [PubMed]
112. Hegde, S.S.; Lokhandwala, M.F. Stimulation of Renal Dopamine Production during Acute Volume Expansion Requires the Presence of Intact Vagi but Not Renal Nerves. *Clin. Exp. Hypertens. A* **1992**, *14*, 1169–1187. [CrossRef] [PubMed]
113. Stephenson, R.K.; Sole, M.J.; Baines, A.D. Neural and Extraneural Catecholamine Production by Rat Kidneys. *Am. J. Physiol.* **1982**, *242*, F261–F266. [CrossRef]
114. Ball, S.G.; Gunn, I.G.; Douglas, I.H. Renal Handling of Dopa, Dopamine, Norepinephrine, and Epinephrine in the Dog. *Am. J. Physiol.* **1982**, *242*, F56–F62. [CrossRef]
115. Boren, D.R.; Henry, D.P.; Selkurt, E.E.; Weinberger, M.H. Renal Modulation of Urinary Catecholamine Excretion during Volume Expansion in the Dog. *Hypertension* **1980**, *2*, 383–389. [CrossRef]
116. Grossman, E.; Hoffman, A.; Armando, I.; Abassi, Z.; Kopin, I.J.; Goldstein, D.S. Sympathoadrenal Contribution to Plasma Dopa (3,4-Dihydroxyphenylalanine) in Rats. *Clin. Sci.* **1992**, *83*, 65–74. [CrossRef] [PubMed]
117. Suzuki, H.; Nakane, H.; Kawamura, M.; Yoshizawa, M.; Takeshita, E.; Saruta, T. Excretion and Metabolism of Dopa and Dopamine by Isolated Perfused Rat Kidney. *Am. J. Physiol.* **1984**, *247*, E285–E290. [CrossRef] [PubMed]
118. Wolfovitz, E.; Grossman, E.; Folio, C.J.; Keiser, H.R.; Kopin, I.J.; Goldstein, D.S. Derivation of Urinary Dopamine from Plasma Dihydroxyphenylalanine in Humans. *Clin. Sci.* **1993**, *84*, 549–557. [CrossRef]
119. Zimlichman, R.; Levinson, P.D.; Kelly, G.; Stull, R.; Keiser, H.R.; Goldstein, D.S. Derivation of Urinary Dopamine from Plasma Dopa. *Clin. Sci.* **1988**, *75*, 515–520. [CrossRef]
120. Baines, A.D.; Chan, W. Production of Urine Free Dopamine from DOPA; a Micropuncture Study. *Life Sci.* **1980**, *26*, 253–259. [CrossRef] [PubMed]
121. Baines, A.D.; Drangova, R.; Hatcher, C. Dopamine Production by Isolated Glomeruli and Tubules from Rat Kidneys. *Can. J. Physiol. Pharmacol.* **1985**, *63*, 155–158. [CrossRef]
122. Eisenhofer, G.; Goldstein, D.S.; Ropchak, T.G.; Kopin, I.J. Source and Physiological Significance of Plasma 3,4-Dihydroxyphenylalanine in the Rat. *J. Neurochem.* **1988**, *51*, 1204–1213. [CrossRef] [PubMed]
123. Eldrup, E.; Hetland, M.L.; Christensen, N.J. Increase in Plasma 3,4-Dihydroxyphenylalanine (DOPA) Appearance Rate after Inhibition of DOPA Decarboxylase in Humans. *Eur. J. Clin. Investig.* **1994**, *24*, 205–211. [CrossRef] [PubMed]
124. Goldstein, D.S.; Holmes, C.; Cannon, R.O.; Eisenhofer, G.; Kopin, I.J. Sympathetic Cardioneuropathy in Dysautonomias. *N. Engl. J. Med.* **1997**, *336*, 696–702. [CrossRef] [PubMed]
125. Goldstein, D.S.; Udelsman, R.; Eisenhofer, G.; Stull, R.; Keiser, H.R.; Kopin, I.J. Neuronal Source of Plasma Dihydroxyphenylalanine. *J. Clin. Endocrinol. Metab.* **1987**, *64*, 856–861. [CrossRef]
126. Pinho, M.J.; Serrão, M.P.; Gomes, P.; Hopfer, U.; Jose, P.A.; Soares-da-Silva, P. Over-expression of renal LAT1 and LAT2 and enhanced L-DOPA uptake in SHR immortalized renal proximal tubular cells. *Kidney Int.* **2004**, *66*, 216–226. [CrossRef]
127. Pinho, M.J.; Gomes, P.; Serrão, M.P.; Bonifácio, M.J.; Soares-da-Silva, P. Organ-specific overexpression of renal LAT2 and enhanced tubular L-DOPA uptake precede the onset of hypertension. *Hypertension.* **2003**, *42*, 613–618. [CrossRef]
128. Wu, Y.; Yin, Q.; Lin, S.; Huang, X.; Xia, Q.; Chen, Z.; Zhang, X.; Yang, D. Increased SLC7A8 expression mediates L-DOPA uptake by renal tubular epithelial cells. *Mol. Med. Rep.* **2017**, *16*, 887–893. [CrossRef]
129. Jiang, X.; Zhang, Y.; Yang, Y.; Yang, J.; Asico, L.D.; Chen, W.; Felder, R.A.; Armando, I.; Jose, P.A.; Yang, Z. Gastrin stimulates renal dopamine production by increasing the renal tubular uptake of l-DOPA. *Am. J. Physiol. Endocrinol. Metab.* **2017**, *312*, E1–E10. [CrossRef]
130. Hoeger, S.; Reisenbuechler, A.; Gottmann, U.; Doyon, F.; Braun, C.; Kaya, Z.; Seelen, M.A.; van Son, W.J.; Waldherr, R.; Schnuelle, P.; et al. Donor Dopamine Treatment in Brain Dead Rats Is Associated with an Improvement in Renal Function Early after Transplantation and a Reduction in Renal Inflammation. *Transpl. Int.* **2008**, *21*, 1072–1080. [CrossRef]
131. Zhang, M.Z.; Yao, B.; Wang, S.; Fan, X.; Wu, G.; Yang, H.; Yin, H.; Yang, S.; Harris, R.C. Intrarenal dopamine deficiency leads to hypertension and decreased longevity in mice. *J. Clin. Investig.* **2011**, *121*, 2845–2854. [CrossRef]

132. Yang, S.; Yao, B.; Zhou, Y.; Yin, H.; Zhang, M.-Z.; Harris, R.C. Intrarenal Dopamine Modulates Progressive Angiotensin II-Mediated Renal Injury. *Am. J. Physiol. Ren. Physiol.* **2012**, *302*, F742–F749. [CrossRef]
133. Zhang, M.Z.; Yao, B.; Yang, S.; Yang, H.; Wang, S.; Fan, X.; Yin, H.; Fogo, A.B.; Moeckel, G.W.; Harris, R.C. Intrarenal dopamine inhibits progression of diabetic nephropathy. *Diabetes* **2012**, *61*, 2575–2584. [CrossRef]
134. Baradaran, A.; Nasri, H.; Rafieian-Kopaei, M. Oxidative Stress and Hypertension: Possibility of Hypertension Therapy with Antioxidants. *J. Res. Med. Sci.* **2014**, *19*, 358–367. [PubMed]
135. Rodrigo, R.; González, J.; Paoletto, F. The Role of Oxidative Stress in the Pathophysiology of Hypertension. *Hypertens. Res.* **2011**, *34*, 431–440. [CrossRef]
136. Sedeek, M.; Hébert, R.L.; Kennedy, C.R.; Burns, K.D.; Touyz, R.M. Molecular Mechanisms of Hypertension: Role of Nox Family NADPH Oxidases. *Curr. Opin. Nephrol. Hypertens.* **2009**, *18*, 122–127. [CrossRef] [PubMed]
137. Santillo, M.; Colantuoni, A.; Mondola, P.; Guida, B.; Damiano, S. NOX Signaling in Molecular Cardiovascular Mechanisms Involved in the Blood Pressure Homeostasis. *Front. Physiol.* **2015**, *6*, 194. [CrossRef]
138. Farooqui, Z.; Mohammad, R.S.; Lokhandwala, M.F.; Banday, A.A. Nrf2 inhibition induces oxidative stress, renal inflammation and hypertension in mice. *Clin. Exp. Hypertens.* **2021**, *43*, 175–180. [CrossRef] [PubMed]
139. Banday, A.A.; Fazili, F.R.; Lokhandwala, M.F. Oxidative stress causes renal dopamine D1 receptor dysfunction and hypertension via mechanisms that involve nuclear factor-kappaB and protein kinase C. *J. Am. Soc. Nephrol.* **2007**, *18*, 1446–1457. [CrossRef]
140. Dikalova, A.E.; Góngora, M.C.; Harrison, D.G.; Lambeth, J.D.; Dikalov, S.; Griendling, K.K. Upregulation of Nox1 in Vascular Smooth Muscle Leads to Impaired Endothelium-Dependent Relaxation via eNOS Uncoupling. *Am. J. Physiol. Heart Circ. Physiol.* **2010**, *299*, H673–H679. [CrossRef]
141. Wind, S.; Beuerlein, K.; Armitage, M.E.; Taye, A.; Kumar, A.H.S.; Janowitz, D.; Neff, C.; Shah, A.M.; Wingler, K.; Schmidt, H.H.H.W. Oxidative Stress and Endothelial Dysfunction in Aortas of Aged Spontaneously Hypertensive Rats by NOX1/2 Is Reversed by NADPH Oxidase Inhibition. *Hypertension* **2010**, *56*, 490–497. [CrossRef]
142. Armando, I.; Wang, X.; Villar, V.A.M.; Jones, J.E.; Asico, L.D.; Escano, C.; Jose, P.A. Reactive Oxygen Species-Dependent Hypertension in Dopamine D2 Receptor-Deficient Mice. *Hypertension* **2007**, *49*, 672–678. [CrossRef] [PubMed]
143. Yang, Y.; Zhang, Y.; Cuevas, S.; Villar, V.A.; Escano, C.; Asico, L.; Yu, P.; Grandy, D.K.; Felder, R.A.; Armando, I.; et al. Paraoxonase 2 decreases renal reactive oxygen species production, lowers blood pressure, and mediates dopamine D2 receptor-induced inhibition of NADPH oxidase. *Free Radic. Biol. Med.* **2012**, *53*, 437–446. [CrossRef] [PubMed]
144. Yang, Y.; Cuevas, S.; Yang, S.; Villar, V.A.; Escano, C.; Asico, L.; Yu, P.; Jiang, X.; Weinman, E.J.; Armando, I.; et al. Sestrin2 decreases renal oxidative stress, lowers blood pressure, and mediates dopamine D2 receptor-induced inhibition of reactive oxygen species production. *Hypertension* **2014**, *64*, 825–832. [CrossRef]
145. Yasunari, K.; Kohno, M.; Kano, H.; Minami, M.; Yoshikawa, J. Dopamine as a Novel Antioxidative Agent for Rat Vascular Smooth Muscle Cells through Dopamine D(1)-like Receptors. *Circulation* **2000**, *101*, 2302–2308. [CrossRef] [PubMed]
146. Yu, P.; Han, W.; Villar, V.A.M.; Li, H.; Arnaldo, F.B.; Concepcion, G.P.; Felder, R.A.; Quinn, M.T.; Jose, P.A. Dopamine D1 Receptor-Mediated Inhibition of NADPH Oxidase Activity in Human Kidney Cells Occurs via Protein Kinase A-Protein Kinase C Cross Talk. *Free Radic. Biol. Med.* **2011**, *50*, 832–840. [CrossRef] [PubMed]
147. Yang, Z.; Asico, L.D.; Yu, P.; Wang, Z.; Jones, J.E.; Bai, R.-K.; Sibley, D.R.; Felder, R.A.; Jose, P.A. D5 Dopamine Receptor Regulation of Phospholipase D. *Am. J. Physiol. Heart Circ. Physiol.* **2005**, *288*, H55–H61. [CrossRef]
148. Yang, Z.; Asico, L.D.; Yu, P.; Wang, Z.; Jones, J.E.; Escano, C.S.; Wang, X.; Quinn, M.T.; Sibley, D.R.; Romero, G.G.; et al. D5 Dopamine Receptor Regulation of Reactive Oxygen Species Production, NADPH Oxidase, and Blood Pressure. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2006**, *290*, R96–R104. [CrossRef] [PubMed]
149. Amatya, B.; Yang, S.; Yu, P.; Vaz de Castro, P.A.S.; Armando, I.; Zeng, C.; Felder, R.A.; Asico, L.D.; Jose, P.A.; Lee, H. Peroxiredoxin-4 and dopamine D5 receptor interact to reduce oxidative stress and inflammation in the kidney. *Antioxid. Redox Signal.* **2023**, *38*, 1150–1166. [CrossRef]
150. Choi, M.R.; Correa, A.H.; del Valle Turco, V.; Garcia, F.A.; Fernández, B.E. Angiotensin II Regulates Extraneuronal Dopamine Uptake in the Kidney. *Nephron Physiol.* **2006**, *104*, 136–143. [CrossRef]
151. Yamaguchi, I.; Yao, L.; Sanada, H.; Ozono, R.; Mouradian, M.M.; Jose, P.A.; Carey, R.M.; Felder, R.A. Dopamine D1A receptors and renin release in rat juxtaglomerular cells. *Hypertension* **1997**, *29*, 962–9688. [CrossRef]
152. Asico, L.D.; Ladines, C.; Fuchs, S.; Accili, D.; Carey, R.M.; Semeraro, C.; Pocchiari, F.; Felder, R.A.; Eisner, G.M.; Jose, P.A. Disruption of the Dopamine D3 Receptor Gene Produces Renin-Dependent Hypertension. *J. Clin. Investig.* **1998**, *102*, 493–498. [CrossRef]
153. Asico, L.; Zhang, X.; Jiang, J.; Cabrera, D.; Escano, C.S.; Sibley, D.R.; Wang, X.; Yang, Y.; Mannon, R.; Jones, J.E.; et al. Lack of Renal Dopamine D5 Receptors Promotes Hypertension. *J. Am. Soc. Nephrol.* **2011**, *22*, 82–89. [CrossRef]
154. Zeng, C.; Luo, Y.; Asico, L.D.; Hopfer, U.; Eisner, G.M.; Felder, R.A.; Jose, P.A. Perturbation of D1 Dopamine and AT1 Receptor Interaction in Spontaneously Hypertensive Rats. *Hypertension* **2003**, *42*, 787–792. [CrossRef] [PubMed]
155. Cheng, H.F.; Becker, B.N.; Harris, R.C. Dopamine Decreases Expression of Type-1 Angiotensin II Receptors in Renal Proximal Tubule. *J. Clin. Investig.* **1996**, *97*, 2745–2752. [CrossRef]
156. Bek, M.J.; Wang, X.; Asico, L.D.; Jones, J.E.; Zheng, S.; Li, X.; Eisner, G.M.; Grandy, D.K.; Carey, R.M.; Soares-da-Silva, P.; et al. Angiotensin-II Type 1 Receptor-Mediated Hypertension in D4 Dopamine Receptor-Deficient Mice. *Hypertension* **2006**, *47*, 288–295. [CrossRef]

157. Zeng, C.; Liu, Y.; Wang, Z.; He, D.; Huang, L.; Yu, P.; Zheng, S.; Jones, J.E.; Asico, L.D.; Hopfer, U.; et al. Activation of D3 Dopamine Receptor Decreases Angiotensin II Type 1 Receptor Expression in Rat Renal Proximal Tubule Cells. *Circ. Res.* **2006**, *99*, 494–500. [CrossRef]
158. Banday, A.A.; Diaz, A.D.; Lokhandwala, M. Kidney Dopamine D1-like Receptors and Angiotensin 1-7 Interaction Inhibits Renal Na+ Transporters. *Am. J. Physiol. Renal Physiol.* **2019**, *317*, F949–F956. [CrossRef]
159. Zhang, Y.; Cuevas, S.; Asico, L.D.; Escano, C.; Yang, Y.; Pascua, A.M.; Wang, X.; Jones, J.E.; Grandy, D.; Eisner, G.; et al. Deficient Dopamine D2 Receptor Function Causes Renal Inflammation Independently of High Blood Pressure. *PLoS ONE* **2012**, *7*, e38745. [CrossRef] [PubMed]
160. Konkalmatt, P.R.; Asico, L.D.; Zhang, Y.; Yang, Y.; Drachenberg, C.; Zheng, X.; Han, F.; Jose, P.A.; Armando, I. Renal Rescue of Dopamine D2 Receptor Function Reverses Renal Injury and High Blood Pressure. *JCI Insight* **2016**, *1*, e85888. [CrossRef] [PubMed]
161. Kumar, M.; Konkalmatt, P.; Asico, L.D.; Hunt, J.; Latham, P.; Jose, P.A.; Armando, I. Dopamine D2 Receptor Specific Deletion in the Renal Proximal Tubules Increases Blood Pressure in Males but Not Female Mice. *Circulation* **2019**, *140* (Suppl. S1), A15988.
162. Wang, Y.; Tay, Y.C.; Harris, D.C. Proximal tubule cells stimulated by lipopolysaccharide inhibit macrophage activation. *Kidney Int.* **2004**, *66*, 655–662. [CrossRef] [PubMed]
163. Guijarro, C.; Egido, J. Transcription factor kappa B (NF-kappa B) and renal disease. *Kidney Int.* **2001**, *59*, 415–424. [CrossRef] [PubMed]
164. Therrien, F.J.; Agharazii, M.; Lebel, M.; Larivière, R. Neutralization of tumor necrosis factor-alpha reduces renal fibrosis and hypertension in rats with renal failure. *Am. J. Nephrol.* **2012**, *36*, 151–161. [CrossRef] [PubMed]
165. Zhang, Y.; Jiang, X.; Qin, C.; Cuevas, S.; Jose, P.A.; Armando, I. Dopamine D2 Receptors' Effects on Renal Inflammation Are Mediated by Regulation of PP2A Function. *Am. J. Physiol. Renal Physiol.* **2016**, *310*, F128–F134. [CrossRef]
166. Beaulieu, J.M.; Gainetdinov, R.R. The physiology, signaling and pharmacology of dopamine receptors. *Pharm. Rev.* **2011**, *63*, 182–217. [CrossRef] [PubMed]
167. Beaulieu, J.M.; Gainetdinov, R.R.; Caron, M.G. The Akt-GSK-3 signaling cascade in the actions of dopamine. *Trends Pharmacol. Sci.* **2007**, *28*, 166172. [CrossRef]
168. Han, F.; Konkalmatt, P.; Mokashi, C.; Kumar, M.; Zhang, Y.; Ko, A.; Farino, Z.J.; Asico, L.D.; Xu, G.; Gildea, J.; et al. Dopamine D2 Receptor Modulates Wnt Expression and Control of Cell Proliferation. *Sci. Rep.* **2019**, *9*, 16861. [CrossRef]
169. Fang, Y.J.; Thomas, G.N.; Xu, Z.L.; Fang, J.Q.; Critchley, J.A.; Tomlinson, B. An affected pedigree member analysis of linkage between the dopamine D2 receptor gene TaqI polymorphism and obesity and hypertension. *Int. J. Cardiol.* **2005**, *102*, 111–116. [CrossRef]
170. Thompson, J.; Thomas, N.; Singleton, A.; Piggott, M.; Lloyd, S.; Perry, E.K.; Morris, C.M.; Perry, R.H.; Ferrier, I.N.; Court, J.A. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: Reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics* **1997**, *7*, 479–484. [CrossRef]
171. Jönsson, E.G.; Nöthen, M.M.; Grünhage, F.; Farde, L.; Nakashima, Y.; Propping, P.; Sedvall, G.C. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Mol. Psychiatry* **1999**, *4*, 290–296. [CrossRef]
172. Duan, J.; Wainwright, M.S.; Comeron, J.M.; Saitou, N.; Sanders, A.R.; Gelernter, J.; Gejman, P.V. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. *Hum. Mol. Genet.* **2003**, *12*, 205–216. [CrossRef] [PubMed]
173. Noble, E.P.; Blum, K.; Ritchie, T.; Montgomery, A.; Sheridan, P.J. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch. Gen. Psychiatry* **1991**, *48*, 648–654. [CrossRef] [PubMed]
174. Rajeevan, H.; Soundararajan, U.; Kidd, J.R.; Pakstis, A.J.; Kidd, K.K. ALFRED: An allele frequency resource for research and teaching. *Nucleic Acids Res.* **2012**, *40*, D1010–D1015. [CrossRef] [PubMed]
175. Jiang, X.; Konkalmatt, P.; Yang, Y.; Gildea, J.; Jones, J.E.; Cuevas, S.; Felder, R.A.; Jose, P.A.; Armando, I. Single-Nucleotide Polymorphisms of the Dopamine D2 Receptor Increase Inflammation and Fibrosis in Human Renal Proximal Tubule Cells. *Hypertension* **2014**, *63*, e74–e80. [CrossRef] [PubMed]
176. Han, F.; Konkalmatt, P.; Chen, J.; Gildea, J.; Felder, R.A.; Jose, P.A.; Armando, I. MiR-217 Mediates the Protective Effects of the Dopamine D2 Receptor on Fibrosis in Human Renal Proximal Tubule Cells. *Hypertension* **2015**, *65*, 1118–1125. [CrossRef] [PubMed]
177. Prasad, P.; Kumar, K.M.; Ammini, A.C.; Gupta, A.; Gupta, R.; Thelma, B.K. Association of dopaminergic pathway gene polymorphisms with chronic renal insufficiency among Asian Indians with type-2 diabetes. *BMC Genet.* **2008**, *9*, 26. [CrossRef]
178. O'Seaghdha, C.M.; Fox, C.S. Genetics of chronic kidney disease. *Nephron Clin. Pract.* **2011**, *118*, c55–c63. [CrossRef]
179. McKnight, A.J.; Currie, D.; Maxwell, A.P. Unravelling the genetic basis of renal diseases; from single gene to multifactorial disorders. *J. Pathol.* **2010**, *220*, 198–216. [CrossRef]
180. Garrett, M.R.; Pezzolesi, M.G.; Korstanje, R. Integrating human and rodent data to identify the genetic factors involved in chronic kidney disease. *J. Am. Soc. Nephrol.* **2010**, *21*, 398–405. [CrossRef]
181. Wetmore, J.B.; Hung, A.M.; Lovett, D.H.; Sen, S.; Quershy, O.; Johansen, K.L. Interleukin-1 gene cluster polymorphisms predict risk of ESRD. *Kidney Int.* **2005**, *68*, 278–284. [CrossRef]

182. Doi, K.; Noiri, E.; Nakao, A.; Fujita, T.; Kobayashi, S.; Tokunaga, K. Functional polymorphisms in the vascular endothelial growth factor gene are associated with development of end-stage renal disease in males. *J. Am. Soc. Nephrol.* **2006**, *17*, 823–830. [CrossRef] [PubMed]
183. Lira, S.S.; Ahammad, I. A comprehensive in silico investigation into the nsSNPs of *Drd2* gene predicts significant functional consequences in dopamine signaling and pharmacotherapy. *Sci. Rep.* **2021**, *11*, 23212. [CrossRef] [PubMed]
184. Ritchie, T.; Noble, E.P. Association of Seven Polymorphisms of the D2 Dopamine Receptor Gene with Brain Receptor-Binding Characteristics. *Neurochem. Res.* **2003**, *28*, 73–82. [CrossRef]
185. Pohjalainen, T.; Rinne, J.O.; Någren, K.; Lehikoinen, P.; Anttila, K.; Syvälahti, E.K.; Hietala, J. The A1 Allele of the Human D2 Dopamine Receptor Gene Predicts Low D2 Receptor Availability in Healthy Volunteers. *Mol. Psychiatry* **1998**, *3*, 256–260. [CrossRef] [PubMed]
186. Mullally, J.A.; Chung, W.K.; LeDuc, C.A.; Reid, T.J.; Febres, G.; Holleran, S.; Ramakrishnan, R.; Korner, J. Weight-loss response to naltrexone/bupropion is modulated by the Taq1A genetic variant near DRD2 (rs1800497): A pilot study. *Diabetes Obes. Metab.* **2021**, *23*, 850–853. [CrossRef]
187. Thomas, G.N.; Tomlinson, B.; Critchley, J.A. Modulation of blood pressure and obesity with the dopamine D2 receptor gene TaqI polymorphism. *Hypertension* **2000**, *36*, 177–182. [CrossRef] [PubMed]
188. Comings, D.E.; Gade, R.; MacMurray, J.P.; Mulhalman, D.; Peters, W.R. Genetic variants of the human obesity (OB) gene: Association with body mass index in young women, psychiatric symptoms, and interaction with the dopamine D2 receptor (DRD2) gene. *Mol. Psychiatry* **1996**, *1*, 325–335.
189. Noble, E.P.; Noble, R.E.; Ritchie, T.; Grandy, D.K.; Sparkes, R.S. Allelic association of the human D2 dopamine receptor gene with obesity. *Int. J. Eat. Disord.* **1994**, *15*, 205–217. [CrossRef]
190. Spitz, M.R.; Detry, M.A.; Pillow, P.; Hu, Y.H.; Amos, C.I.; Hong, W.K.; Wu, X.F. Variant alleles of the D2 dopamine receptor gene and obesity. *Nutrition Res.* **2000**, *20*, 371–380. [CrossRef]
191. Barnard, N.D.; Noble, E.P.; Ritchie, T.; Cohen, J.; Jenkins, D.J.; Turner-McGrievy, G.; Gloede, L.; Green, A.A.; Ferdowsian, H. D2 dopamine receptor Taq1A polymorphism, body weight, and dietary intake in type 2 diabetes. *Nutrition* **2009**, *25*, 58–65. [CrossRef]
192. Hirvonen, M.M.; Lumme, V.; Hirvonen, J.; Pesonen, U.; Någren, K.; Vahlberg, T.; Scheinin, H.; Hietala, J. C957T Polymorphism of the Human Dopamine D2 Receptor Gene Predicts Extrastriatal Dopamine Receptor Availability in vivo. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2009**, *33*, 630–636. [CrossRef] [PubMed]
193. Hirvonen, M.M.; Laakso, A.; Någren, K.; Rinne, J.O.; Pohjalainen, T.; Hietala, J. C957T Polymorphism of Dopamine D2 Receptor Gene Affects Striatal DRD2 in Vivo Availability by Changing the Receptor Affinity. *Synapse* **2009**, *63*, 907–912. [CrossRef] [PubMed]
194. Hirvonen, M.; Laakso, A.; Någren, K.; Rinne, J.O.; Pohjalainen, T.; Hietala, J. C957T Polymorphism of the Dopamine D2 Receptor (DRD2) Gene Affects Striatal DRD2 Availability in Vivo. *Mol. Psychiatry* **2004**, *9*, 1060–1061. [CrossRef] [PubMed]
195. Lawford, B.R.; Barnes, M.; Morris, C.P.; Noble, E.P.; Nyst, P.; Heslop, K.; Young, R.M.; Voisey, J.; Connor, J.P. Dopamine 2 Receptor Genes Are Associated with Raised Blood Glucose in Schizophrenia. *Can. J. Psychiatry* **2016**, *61*, 291–297. [CrossRef]
196. Gildea, J.J.; Xu, P.; Schiermeyer, K.A.; Yue, W.; Carey, R.M.; Jose, P.A.; Felder, R.A. Inverse Salt Sensitivity of Blood Pressure Is Associated with an Increased Renin-Angiotensin System Activity. *Biomedicines* **2022**, *10*, 2811. [CrossRef]
197. Amin, M.; Wu, R.; Postolache, T.T.; Gragnoli, C. Linkage and association of novel DRD2 variants to the comorbidity of type 2 diabetes and depression. *Eur. Rev. Med. Pharmacol. Sci.* **2022**, *26*, 8370–8375. [CrossRef]
198. Li, T.; Arranz, M.; Aitchison, K.J.; Bryant, C.; Liu, X.; Kerwin, R.W.; Murray, R.; Sham, P.; Collier, D.A. Case-Control, Haplotype Relative Risk and Transmission Disequilibrium Analysis of a Dopamine D2 Receptor Functional Promoter Polymorphism in Schizophrenia. *Schizophr. Res.* **1998**, *32*, 87–92.
199. Moyer, R.A.; Wang, D.; Papp, A.C.; Smith, R.M.; Duque, L.; Mash, D.C.; Sadee, W. Intronic Polymorphisms Affecting Alternative Splicing of Human Dopamine D2 Receptor Are Associated with Cocaine Abuse. *Neuropsychopharmacology* **2011**, *36*, 753–762. [CrossRef]
200. Kaalund, S.S.; Newburn, E.N.; Ye, T.; Tao, R.; Li, C.; Deep-Soboslay, A.; Herman, M.M.; Hyde, T.M.; Weinberger, D.R.; Lipska, B.K.; et al. Contrasting Changes in DRD1 and DRD2 Splice Variant Expression in Schizophrenia and Affective Disorders, and Associations with SNPs in Postmortem Brain. *Mol. Psychiatry* **2014**, *19*, 1258–1266. [CrossRef]
201. Cohen, O.S.; Weickert, T.W.; Hess, J.L.; Paish, L.M.; McCoy, S.Y.; Rothmond, D.A.; Galletly, C.; Liu, D.; Weinberg, D.D.; Huang, X.-F.; et al. A Splicing-Regulatory Polymorphism in DRD2 Disrupts ZRANB2 Binding, Impairs Cognitive Functioning and Increases Risk for Schizophrenia in Six Han Chinese Samples. *Mol. Psychiatry* **2016**, *21*, 975–982. [CrossRef]
202. Bertolino, A.; Fazio, L.; Di Giorgio, A.; Blasi, G.; Romano, R.; Taurisano, P.; Caforio, G.; Sinibaldi, L.; Ursini, G.; Popolizio, T.; et al. Genetically Determined Interaction between the Dopamine Transporter and the D2 Receptor on Prefronto-Striatal Activity and Volume in Humans. *J. Neurosci.* **2009**, *29*, 1224–1234. [CrossRef]
203. Bertolino, A.; Taurisano, P.; Pisciotta, N.M.; Blasi, G.; Fazio, L.; Romano, R.; Gelao, B.; Lo Bianco, L.; Lozupone, M.; Di Giorgio, A.; et al. Genetically Determined Measures of Striatal D2 Signaling Predict Prefrontal Activity during Working Memory Performance. *PLoS ONE* **2010**, *5*, e9348. [CrossRef] [PubMed]

204. Zhang, Y.; Bertolino, A.; Fazio, L.; Blasi, G.; Rampino, A.; Romano, R.; Lee, M.L.; Xiao, T.; Papp, A.; Wang, D.; et al. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20552–20557. [CrossRef] [PubMed]
205. Cravchik, A.; Sibley, D.R.; Gejman, P.V. Functional Analysis of the Human D2 Dopamine Receptor Missense Variants. *J. Biol. Chem.* **1996**, *271*, 26013–26017. [CrossRef]
206. Doehring, A.; Kirchhof, A.; Lötsch, J. Genetic diagnostics of functional variants of the human dopamine D2 receptor gene. *Psychiatr. Genet.* **2009**, *19*, 259–268. [CrossRef] [PubMed]
207. Laursen, T.M.; Munk-Olsen, T.; Vestergaard, M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr. Opin. Psychiatry* **2012**, *25*, 83–98. [CrossRef] [PubMed]
208. Tzeng, N.S.; Hsu, Y.H.; Ho, S.Y.; Kuo, Y.C.; Lee, H.C.; Yin, Y.J.; Chen, H.A.; Chen, W.L.; Chu, W.C.C.; Huang, H.L. Is schizophrenia associated with an increased risk of chronic kidney disease? A nationwide matched cohort study. *BMJ Open* **2015**, *5*, e006777. [CrossRef]
209. Højlund, M.; Lund, L.C.; Herping, J.L.E.; Haastrup, M.B.; Damkier, P.; Henriksen, D.P. Second-generation antipsychotics and the risk of chronic kidney disease: A population-based case-control study. *BMJ Open* **2020**, *10*, e038247. [CrossRef]
210. Jiang, Y.; McCombs, J.S.; Park, S.H. A Retrospective Cohort Study of Acute Kidney Injury Risk Associated with Antipsychotics. *CNS Drugs* **2017**, *31*, 319–326. [CrossRef]
211. Ermakov, E.A.; Melamud, M.M.; Boiko, A.S.; Kamaeva, D.A.; Ivanova, S.A.; Nevinsky, G.A.; Buneva, V.N. Association of Peripheral Inflammatory Biomarkers and Growth Factors Levels with Sex, Therapy and Other Clinical Factors in Schizophrenia and Patient Stratification Based on These Data. *Brain Sci.* **2023**, *13*, 836. [CrossRef]
212. Kluge, M.; Schuld, A.; Schacht, A.; Himmerich, H.; Dalal, M.A.; Wehmeier, P.M.; Hinze-Selch, D.; Kraus, T.; Dittmann, R.W.; Pollmächer, T. Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever. *Psychoneuroendocrinology* **2009**, *34*, 118–128. [CrossRef] [PubMed]
213. Tourjman, V.; Kouassi, E.; Koue, M.-E.; Rocchetti, M.; Fortin-Fournier, S.; Fusar-Poli, P.; Potvin, S. Antipsychotics' effects on blood levels of cytokines in schizophrenia: A meta-analysis. *Schizophr. Res.* **2013**, *151*, 43–47. [CrossRef] [PubMed]
214. Patlola, S.R.; Donohoe, G.; McKernan, D.P. Anti-inflammatory effects of 2nd generation antipsychotics in patients with schizophrenia: A systematic review and meta-analysis. *J. Psychiatr. Res.* **2023**, *160*, 126–136. [CrossRef] [PubMed]
215. Hwang, Y.J.; Dixon, S.N.; Reiss, J.P.; Wald, R.; Parikh, C.R.; Gandhi, S.; Shariff, S.Z.; Pannu, N.; Nash, D.M.; Rehman, F.; et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: A population-based cohort study. *Ann. Intern. Med.* **2014**, *161*, 242–248. [CrossRef]
216. U.S. Food and Drug Administration. Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. Available online: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm (accessed on 25 April 2013).
217. Burghardt, K.J.; Mando, W.; Seyoum, B.; Yi, Z.; Burghardt, P.R. The effect of antipsychotic treatment on hormonal, inflammatory, and metabolic biomarkers in healthy volunteers: A systematic review and meta-analysis. *Pharmacotherapy* **2022**, *42*, 504–513. [CrossRef]
218. Klemettila, J.P.; Kampman, O.; Seppala, N.; Viikki, M.; Hamalainen, M.; Moilanen, E.; Leinonen, E. Cytokine and adipokine alterations in patients with schizophrenia treated with clozapine. *Psychiatry Res.* **2014**, *218*, 277–283. [CrossRef]
219. Correll, C.U.; Detraux, J.; De Lepeleire, J.; De Hert, M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry* **2015**, *14*, 119–136. [CrossRef]
220. Meyer, J.M.; Correll, C.U. Increased Metabolic Potential, Efficacy, and Safety of Emerging Treatments in Schizophrenia. *CNS Drugs* **2023**, *37*, 545–570. [CrossRef]
221. De Hert, M.; Detraux, J.; van Winkel, R.; Yu, W.; Correll, C.U. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat. Rev. Endocrinol.* **2012**, *8*, 114–126. [CrossRef]
222. Correll, C.U.; Lencz, T.; Malhotra, A.K. Antipsychotic drugs and obesity. *Trends Mol. Med.* **2011**, *17*, 97–107. [CrossRef]
223. Coccurello, R.; Moles, A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: Clues for understanding obesity and novel drug design. *Pharmacol. Ther.* **2010**, *127*, 210–251. [CrossRef] [PubMed]