International Journal of
*Molecular Sciences*

MDPI

*Review*

# Sympathetic Nervous System and Atherosclerosis

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**Abstract:** Atherosclerosis is characterized by the narrowing of the arterial lumen due to subendothelial lipid accumulation, with hypercholesterolemia being a major risk factor. Despite the recent advances in effective lipid-lowering therapies, atherosclerosis remains the leading cause of mortality globally, highlighting the need for additional therapeutic strategies. Accumulating evidence suggests that the sympathetic nervous system plays an important role in atherosclerosis. In this article, we reviewed the sympathetic innervation in the vasculature, norepinephrine synthesis and metabolism, sympathetic activity measurement, and common signaling pathways of sympathetic activation. The focus of this paper was to review the effectiveness of pharmacological antagonists or agonists of adrenoceptors (α1, α2, β1, β2, and β3) and renal denervation on atherosclerosis. All five types of adrenoceptors are present in arterial blood vessels. α1 blockers inhibit atherosclerosis but increase the risk of heart failure while α2 agonism may protect against atherosclerosis and newer generations of β blockers and β3 agonists are promising therapies against atherosclerosis; however, new randomized controlled trials are warranted to investigate the effectiveness of these therapies in atherosclerosis inhibition and cardiovascular risk reduction in the future. The role of renal denervation in atherosclerosis inhibition in humans is yet to be established.

**Keywords:** alpha blocker; beta blocker; blood vessel; sympathetic activity; atherosclerosis; renal denervation



**Citation:** Wang, Y.; Anesi, J.; Maier, M.C.; Myers, M.A.; Oqueli, E.; Sobey, C.G.; Drummond, G.R.; Denton, K.M. Sympathetic Nervous System and Atherosclerosis. *Int. J. Mol. Sci.* **2023**, *24*, 13132. https://doi.org/10.3390/ijms241713132

Academic Editor: David Della-Morte

Received: 6 August 2023
Revised: 18 August 2023
Accepted: 22 August 2023
Published: 23 August 2023



## 1. Introduction

Atherosclerosis is an arterial disease that is characterized by the narrowing of the arterial lumen due to the subendothelial accumulation of lipids [1–3]. Atherosclerosis is the key underlying mechanism for ischemic heart disease and stroke [4]. Despite the availability of a wide array of effective lipid-lowering medications such as statins, ezetimibe, and PCSK9 (proprotein convertase subtilisin-like kexin type 9) inhibitors [5–8], ischemic heart disease and stroke remain the leading two causes of mortality globally [9], highlighting the need to identify new therapeutic strategies for atherosclerosis.

Arteries are innervated organs [10], and the possible contribution of the sympathetic nervous system to atherosclerosis has been highlighted recently [11,12]. In this review, we aimed to summarize the effectiveness of pharmacological antagonists or agonists of adrenergic receptors (α1, α2, β1, β2, and β3 adrenoceptors) and renal denervation on atherosclerosis.

## 2. Sympathetic Innervation in the Vasculature

Major arteries and precapillary arterioles are innervated by sympathetic nerves, but other vessels, such as venules, capillaries, and collecting veins, are rarely innervated [13]. The integration of the sympathetic nervous system's efferent activities to the blood vessels happens in the medulla oblongata of the brainstem, the activities of which are regulated by the hypothalamus and cerebral cortex [14,15].

The sympathetic pathway is formed via two serially connected sets of neurons [16,17] (Figure 1). The first (preganglionic) set of neurons originates in the brainstem or the spinal cord. These sympathetic preganglionic neurons are myelinated. They exit the spinal cord from the ventral roots and synapse with the postganglionic sympathetic neurons (second set) in the ganglia, with acetylcholine as the neurotransmitter. Therefore, the preganglionic sympathetic neurons are cholinergic. The postganglionic neuronal axons travel to the vascular smooth muscle, and the nerve endings branch repeatedly, each branch forming synapses en passant "synapses in passing" with vascular smooth muscle cells [16]. Each nerve ending has a series of varicosities (knoblike swellings) containing mitochondria and synaptic vesicles, which make the nerve endings resemble a string of beads, with the beads ~1 μm wide and separated by ~4 μm [18]. The structure of the sympathetic nerve and smooth muscle synapse has three parts: the presynaptic part (varicosities of the nerve ending), the postsynaptic part (the smooth muscle membrane), and the synaptic cleft (the area between the presynaptic and postsynaptic parts) [19]. The neurotransmitter in the synaptic vesicles of the varicosities is norepinephrine, and, therefore, the postganglionic sympathetic neurons are adrenergic. Exceptions to this are the sympathetic postganglionic neurons to blood vessels in the skin; these neurons secrete acetylcholine and therefore are cholinergic [14]. However, blood vessels in the skin will not be covered by this review as they are not thought to be involved in atherosclerosis.

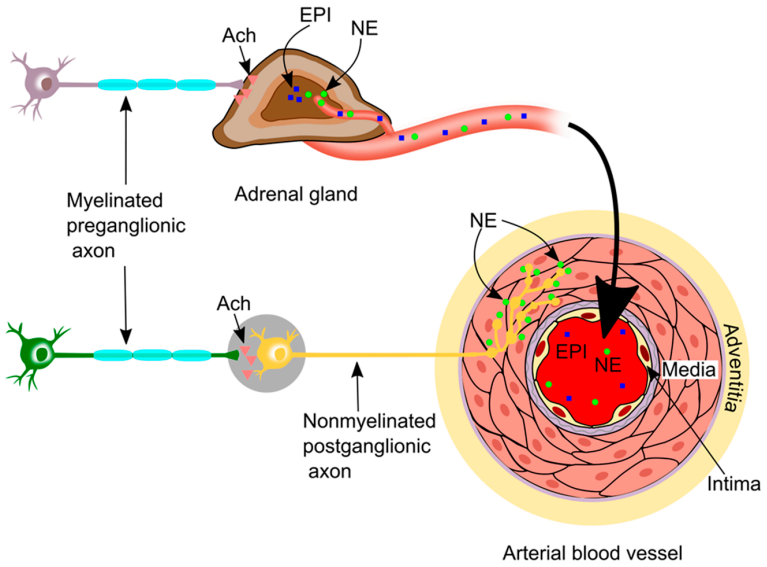


**Figure 1.** Sympathetic innervation in vasculature. The sympathetic pathway is formed of two serially connected sets of neurons: preganglionic and postganglionic neurons. The preganglionic neurons originate in the brainstem or the spinal cord. They exit the spinal cord and synapse (using acetylcholine as a neurotransmitter) with postganglionic sympathetic neurons in the ganglia. The nerve endings of the postganglionic neurons branch repeatedly, forming synapses en passant ("synapses in passing") or varicosities (knoblike swellings) containing mitochondria and synaptic vesicles. The key neurotransmitter in the synaptic vesicles of the varicosities is norepinephrine. In addition, the sympathetic preganglionic neurons synapse with chromaffin cells in the adrenal gland to stimulate the production of epinephrine and norepinephrine from the adrenal medulla. The produced epinephrine and norepinephrine then enter the blood and may affect distant blood vessels and tissues. Ach, acetylcholine; EPI, epinephrine; and NE, norepinephrine.

In addition, the sympathetic preganglionic neurons synapse with chromaffin cells in the adrenal gland. As a result, the adrenal medulla produces epinephrine (80%) and norepinephrine (20%) into circulation [20]. These two hormones (rather than neurotransmitters, as they function in the manner of hormones) enter the blood and circulate around the body [20]. Therefore, circulating epinephrine and norepinephrine can affect distant blood vessels [17]. Norepinephrine induces vasoconstriction in the skin and viscera and shifts blood flow to other areas, such as exercising skeletal muscle. Epinephrine induces vasodilation of the blood vessels in skeletal muscle at the onset of the "fight or flight" response [20].

## 3. Norepinephrine Synthesis and Metabolism

Norepinephrine is synthesized in the postganglionic neurons from tyrosine, which is synthesized from phenylalanine and can also be obtained directly from food (Figure 2). Tyrosine is converted by tyrosine hydroxylase to dihydroxyphenylalanine (DOPA); DOPA, in turn, is converted by DOPA decarboxylase to dopamine in the cytoplasm. Dopamine is taken up into vesicles and converted by dopamine β-hydroxylase to norepinephrine [21]. In the adrenal medulla, norepinephrine is converted by phenylethanolamine N-methyltransferase to epinephrine [20].

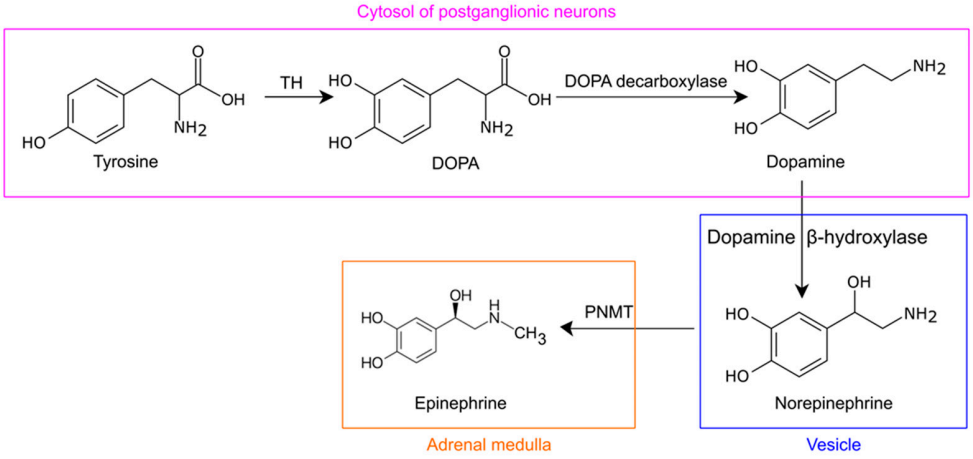


**Figure 2.** Norepinephrine biosynthesis. Tyrosine is converted by tyrosine hydroxylase (TH) to dihydroxyphenylalanine (DOPA), and the latter is converted by DOPA decarboxylase to dopamine in the cytoplasm. Dopamine is converted by dopamine β-hydroxylase to norepinephrine in the vesicles. In the adrenal medulla, norepinephrine is converted by phenylethanolamine N-methyltransferase (PNMT) to epinephrine.

Norepinephrine is stored in vesicles in the nerve terminals, where it is concentrated and protected from metabolism until release upon nerve stimulation. The effects of norepinephrine are terminated mainly through reuptake back into nerve terminals by a high-affinity transporter. Norepinephrine can also be metabolized to inactive products.

Much of the norepinephrine released from adrenergic fibers is removed from the synapse by active transport back into the nerve endings in a process called reuptake [14]. Monoamine oxidase in the mitochondria of the synaptic knob, together with other enzymes, will inactivate norepinephrine [22]. This may take a few seconds, during which some molecules may diffuse into nearby tissues or the bloodstream, where other enzymes decompose them. Some norepinephrine molecules, however, may escape decomposition and remain active for a while. In fact, norepinephrine and epinephrine released from the adrenal medulla upon sympathetic stimulation can exist in the blood for up to 20 min [14].

Norepinephrine is metabolized by various enzymes including monoamine oxidase, catechol-O-methyltransferase, aldehyde reductase, and aldehyde dehydrogenase, and the final products are 3-methoxy-4-hydroxyphenylglycol (MHPG) and 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid) [23–25] (Figure 3). The major metabolite found in the blood

and urine is MHPG [26,27], and levels of this metabolite are frequently used to assess the functional status of the noradrenergic system in human subjects [28].

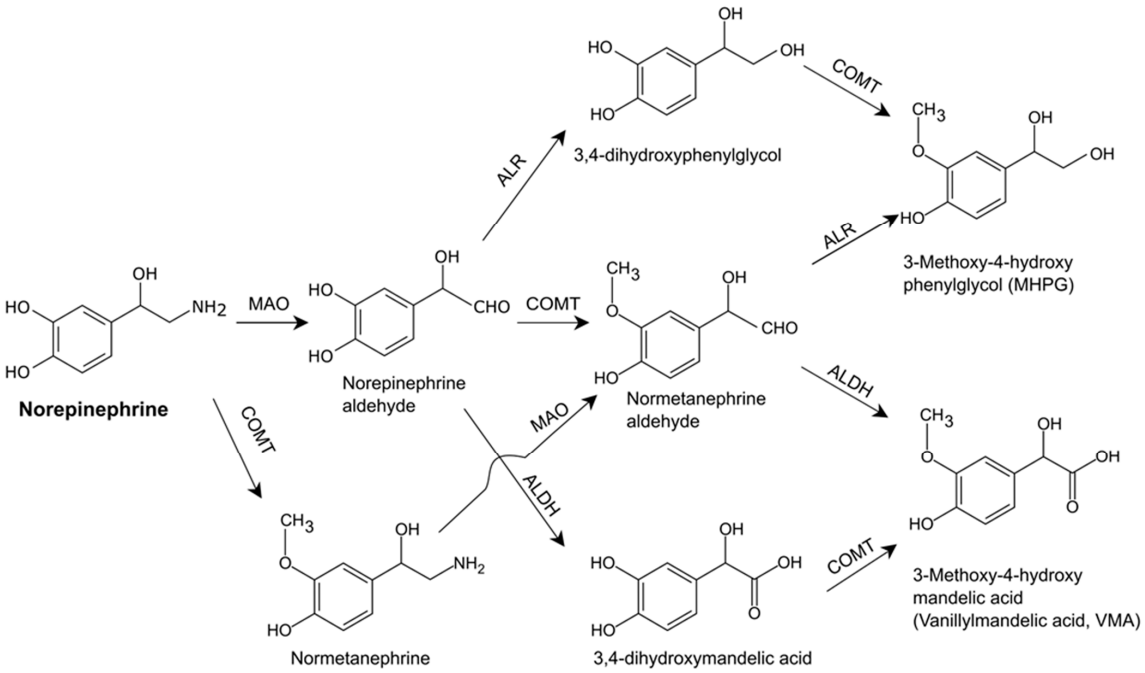


**Figure 3.** Norepinephrine metabolism. ALDH, aldehyde dehydrogenase; ALR, aldehyde reductase; COMT, catechol-O-methyltransferase; and MAO, monoamine oxidase.

## 4. Measurements of Sympathetic Nerve Activity

The methods for measuring the activity of sympathetic nerves can be categorized into those measuring global sympathetic nerve activity and those measuring regional sympathetic nerve activity. Global activity can be measured by assessing the norepinephrine concentration in the blood or urine [29–31], and regional activity can be measured by norepinephrine spill over [32,33], clinical microneurography [34–39], and sympathetic imaging [40–42]. The advantages and disadvantages of these methods are listed in Table 1.

**Table 1.** Methods for measuring sympathetic nerve activity.

| | NE in Blood/Urine | NE Spillover | Clinical Microneurography | Sympathetic Imaging |
|---|---|---|---|---|
| Global/regional measurement | Global | Regional | Regional | Regional |
| Advantages | Convenient<br>Little or no invasiveness | Measures the regional rate of NE spillover from the heart or kidneys | Is the only method for the direct measurement of adrenergic activity in humans<br>Precisely assesses resting sympathetic activity and tracks the changes in cardiovascular regulation in response to stimuli | Demonstrates the anatomy of sympathetic innervation of an organ |
| Disadvantages | Lacks information on regional sympathetic responses | Is highly invasive<br>Requires catheterization of veins draining internal organs | Requires a high degree of skill<br>Requires several months of training | Is unable to differentiate the relative contribution of denervation and dysinnervation |
| References | [29–31] | [32,33] | [34–39] | [40–42] |

NE, norepinephrine.

## 5. Adrenergic Receptors (Adrenoceptors) in the Vasculature

There are two types of adrenoceptors: alpha (α) and beta (β). α adrenoceptors include α1 and α2, and β adrenoceptors include β1, β2, and β3. All of these adrenoceptors are G protein-coupled receptors (GPCRs) with seven transmembrane domains [43,44]. They respond to norepinephrine and epinephrine by producing a response within the cell involving a second messenger or ion channel [43]. Although norepinephrine has a stronger effect on α adrenoceptors, it can stimulate both α and β adrenoceptors. Consequently, the way sympathetic activation influences effector cells depends on the relative numbers of α and β adrenoceptors in the cell membrane [14].

All five types of adrenoceptors are expressed in vasculature [45]. In particular, α1 adrenoceptors are predominately expressed in the peripheral arterial blood vessels [46–48]; β1 adrenoceptors are distributed in the thoracic aorta, carotid, femoral, and pulmonary arteries; β2 adrenoceptors are distributed in the aorta and carotid arteries [49]; and β3 adrenoceptors are distributed in the blood vessels in the skin [50].

These adrenoceptors are also richly expressed in other organs. For example, α1 adrenoceptors are expressed in the airway and urinary tract [51]; β1 adrenoceptors are richly expressed in the heart, kidney, and fat cells [52]; β2 adrenoceptors are located in the bronchial tract, pancreas, uterus, liver, and endocrine glands [53]; and β3 adrenoceptors are located in the urinary bladder [54], brown adipose tissue, white adipose tissue, and myocardium [55].

## 6. Molecular Pathways Underlying Sympathetic Activation-Induced Vasoconstriction and Relaxation

### *6.1. Sympathetic Activation-Induced Vasoconstriction under Physiological Conditions*

The basal sympathetic activity plays a pivotal role in maintaining vascular tone, as a sympathetic ganglionic blockade decreases blood pressure [56]. Consistently, sympathetic activation can increase blood pressure, mediated by vasoconstriction via α adrenoceptor activation [46,57]. Activation of α1 adrenoceptors leads to an increase in the calcium ($Ca^{2+}$) concentration in the cytosol of the vascular smooth muscle cells and consequently triggers a contractile response [58] (Figure 4). First, the binding of norepinephrine or epinephrine to the α1 adrenoceptor (G protein-coupled receptor) leads to the opening of $Ca^{2+}$ channels (L-type and T-type) in the cell membrane of the vascular smooth muscle cells [43,46,58], which increases the cytoplasmic $Ca^{2+}$ concentration ($[Ca^{2+}]_i$). In addition, the G protein Gq/11 activates phospholipase C, which converts phosphatidylinositol 4,5-bisphosphate (PIP2) to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). IP3 will then bind to the IP3 receptor on the sarcoplasmic reticulum (SR) to release stored $Ca^{2+}$. Once $Ca^{2+}$ enters the cell it will bind and activate calmodulin. Calmodulin then activates myosin light chain (MLC) kinase. Phosphorylation of MLC by MLC kinase leads to a conformational change in the myosin head, which increases myosin ATPase activity and promotes interaction between the myosin head and actin. Cross-bridge cycling then occurs, and tension is generated. Dephosphorylation of MLC by MLC phosphatase terminates smooth muscle contraction [58,59].

$[Ca^{2+}]_i$ is vital for the smooth muscle to contract. However, the contractility at a given level of $[Ca^{2+}]_i$ could vary, and under some conditions, the same concentration or even a lower cytoplasmic $Ca^{2+}$ concentration can produce high contractile force. This phenomenon is called $Ca^{2+}$ sensitization [60,61]. In vascular smooth muscle cells, $Ca^{2+}$ sensitization is mediated by protein kinase C (PKC) and Rho kinase via inhibition of MLC phosphatase [60] (Figure 4). DAG, produced by PLC activity, activates PKC which then phosphorylates and inhibits MLC phosphatase [60,62]. In addition, the G12/13 signaling pathway existing in vascular smooth muscle [63] could lead to the activation of Rho and Rho kinase, which then phosphorylates and inhibits MLC phosphatase [62].

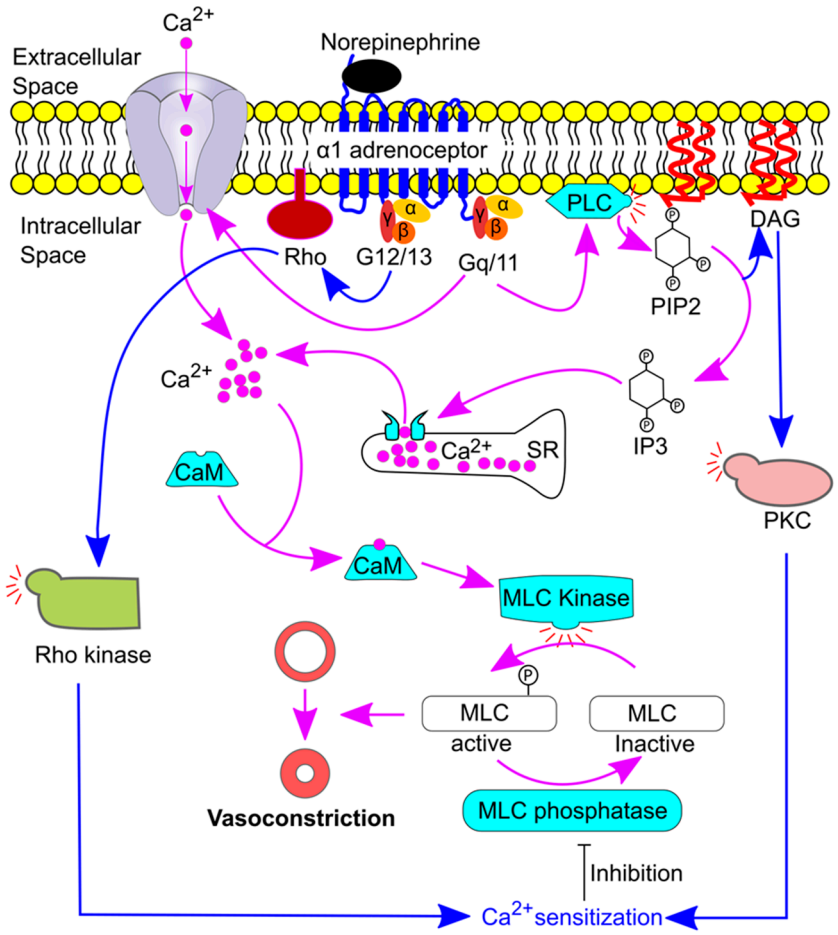


**Figure 4.** Illustration of norepinephrine-induced vasoconstriction via an α1 adrenoceptor. Norepinephrine binds the α1 adrenoceptor, resulting in Gq/11 activation and opening of the calcium ($Ca^{2+}$) channel. Thus, the cytoplasmic $Ca^{2+}$ concentration increases. In addition, Gq/11 induces inositol triphosphate (IP3) production which binds to IP3 receptors on the sarcoplasmic reticulum (SR), resulting in the release of $Ca^{2+}$ from SR. Free $Ca^{2+}$ then binds to calmodulin (CaM) and phosphorylates the myosin light chain (MLC), which leads to vasoconstriction. In addition, activation of the α1 adrenoceptor can lead to the activation of Rho kinase and protein kinase C (PKC), which results in $Ca^{2+}$ sensitization by phosphorylating and inhibiting MLC phosphatase. DAG, diacylglycerol; P, phosphate; and PLC, phospholipase C.

### *6.2. Activation of β Adrenoceptors Induces Vasorelaxation*

Activation of β adrenoceptors by isoproterenol induces vasorelaxation in the thoracic aorta, carotid, femoral, and pulmonary arteries [49,50,64], suggesting that β adrenoceptors play a modulatory role in vascular tone regulation. Activation of β adrenoceptors (GPCR) leads to Gs activation, which activates adenylyl cyclase to increase cyclic adenosine monophosphate (cAMP) [65]. cAMP then activates protein kinase G (PKG), which opens the large-conductance, $Ca^{2+}$-activated potassium ($BK_{Ca}$) channel, thus relaxing the vascular smooth muscle [66]. In large pulmonary arteries, the activation of β adrenoceptors can also increase nitric oxide production by the endothelial cells [67], which leads to vasorelaxation.

## 7. Roles of Adrenoceptors in Atherosclerosis

### *7.1. Role of α1 Adrenoceptors in Atherosclerosis*

α1 blockers have been frequently shown to inhibit atherosclerosis in research animals [68–70] and humans [71], although certain studies fail to demonstrate a beneficial effect of α1 blockers [72]. The anti-atherosclerotic effects of α1 blockers may be mediated by their blood pressure-lowering effect and their favorable effect on lipid profile [68,71–73].

It has been shown that α1 blockers decrease plasma total cholesterol, very low-density lipoprotein (VLDL), and triglycerides [68,71–73], and increase high-density lipoprotein (HDL) cholesterol [71]. Despite these beneficial effects, α1 blockers may increase the risk of heart failure in the long term [74]. The mechanism underlying this side effect is unknown. As α1 adrenoceptors are also expressed in cardiomyocytes [47], it is possible that α1 blockers modify gene expression in cardiomyocytes via the α1 adrenoceptor-stimulatory Gs protein pathway and consequently weaken the structure or function of the heart over a long period of time.

### 7.2. Role of α2 Adrenoceptors in Atherosclerosis

α2 activation leads to activation of the inhibitory Gi protein which inhibits adenylate cyclase and decreases intracellular cAMP [51]. In addition, α2 activation can lead to a decrease in cytoplasmic $Ca^{2+}$, which then leads to a decrease in neurotransmitter release [75]. Both central and peripheral activation of α2 adrenoceptors can reduce sympathetic activity [51].

The involvement of α2 adrenoceptors in atherosclerosis is not clear. A recent study has shown that moxonidine, an agonist for α2 and imidazoline 1 (I1) receptors, inhibits atherosclerosis in apolipoprotein E-deficient ($ApoE^{-/-}$) mice [76], possibly via inhibiting inflammation and promoting oxidized LDL uptake and clearance (Figure 5). This anti-atherosclerotic effect seems to be mediated by α2 adrenoceptors as the effect of moxonidine on oxidized LDL uptake by cultured vascular smooth muscle cells was inhibited by the α2 antagonist RX821002; in addition, activation of I1 by AGN192403 did not replicate the effects of moxonidine on oxidized LDL uptake. The role of α2 adrenoceptors in atherosclerosis needs to be investigated in the future using specific α2-agonists.

### 7.3. Role of β1 Adrenoceptors in Atherosclerosis

Many preclinical [77–83] and clinical studies [84,85] have been conducted in recent years to investigate the effect of β blockers on atherosclerosis (Table 2). It has been shown that the first generation of β blockers (non-selective β1/β2 blockers) [77], the second generation of β blockers (selective β1 blockers) [78,79,84,85], and the third generation of β blockers (β blockers with additional properties) [80–83] attenuate atherosclerosis progression. In particular, two randomized controlled trials showed that the selective β1 blocker metoprolol reduced the rate of atherosclerosis progression [84,85], even in the presence of lipid-lowering therapy [85]. In these two trials, metoprolol was used at a low dose of 25–100 mg daily in a controlled-release/extended-release formulation [84,85].

β blockers inhibit atherosclerosis via multiple mechanisms including inhibiting inflammation (Table 2). For example, the β1-selective blocker metoprolol decreases the circulating level of proinflammatory cytokines and chemokines and decreases the macrophage content in the lesion [79]. Similarly, the non-selective inhibition of β1 and β2 adrenoceptors by propranolol decreases the production of granulocyte-macrophage progenitors (GMPs) in the bone marrow and decreases the circulating numbers of monocytes and neutrophils [77]. The third generation of β blockers has other anti-atherosclerotic mechanisms, including promoting cholesterol efflux [80], inhibiting oxidative stress [81], preventing LDL oxidation [82], improving endothelial function [82,83], and decreasing monocyte adhesion to endothelium [83].

It is worth noting that some studies have shown that β blockers (non-selective β1/β2 blockers or selective β1 blockers) have adverse effects on plasma lipoprotein levels such as increasing VLDL and decreasing HDL cholesterol, and, therefore, β blockers are currently discouraged for use to prevent atherosclerosis [53]. However, recent studies have reported that β blockers do not affect plasma levels of total cholesterol, triglycerides, or HDL cholesterol [79,81,83,86].

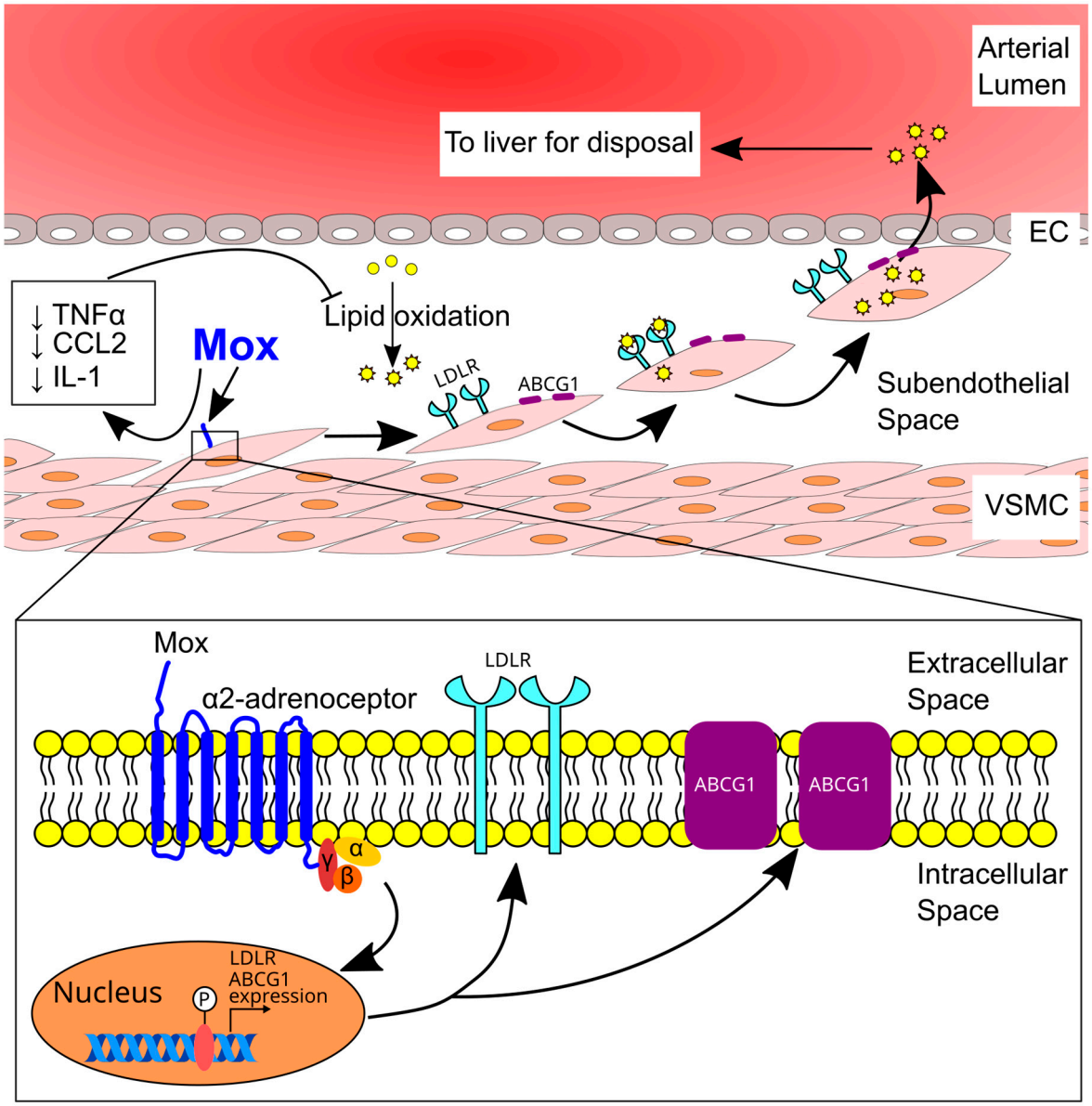


**Figure 5.** Moxonidine-induced inhibition of atherosclerosis. Moxonidine decreases the expression of inflammatory genes, inhibits the oxidation of LDL, and enhances VSMC migration. VSMCs then migrate to a location that could facilitate both oxidized LDL uptake via the LDL receptor and its efflux back to circulation via the ABCG1 transporter for detoxification by the liver. ↓, decrease; ABCG1, ATP binding cassette subfamily G member 1; CCL2, chemokine ligand 2 (also known as monocyte chemoattractant protein-1); EC, endothelial cell; IL, interleukin; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; Mox, moxonidine; TNF-α, tumor necrosis factor-α; and VSMC, vascular smooth muscle cell. This figure is from Wang et al. with permission [76].

In addition, the relationship between the baseline use of β blockers and clinal outcomes in epidemiological studies is inconsistent. For example, it has been reported that baseline β1 blocker use was associated with lower 30-day and 10-year mortality in 3371 patients undergoing major vascular surgery [87]. However, it has also been reported that baseline β blocker use was associated with an increased cardiovascular event risk in 11,785 patients undergoing infrainguinal revascularization for critical limb ischemia [88] and in 14,671 patients with type 2 diabetes and established atherosclerotic cardiovascular disease [89]. Moreover, Cimaglia et al. found that baseline β blocker use was not associated with an increased cardiovascular event risk in 618 diabetic patients with the most advanced stage of

peripheral artery disease [90]. Therefore, more randomized controlled trials are needed to establish the merit of the use of β blockers for atherosclerosis inhibition and cardiovascular risk reduction.

**Table 2.** Effect of β blockers (β1/β2 blockers) on atherosclerosis in recent studies.

| β Blockers | Patients/Animals | Effect on Atherosclerosis | Mechanism | Reference |
|---|---|---|---|---|
| First Generation: Non-Selective β1 and β2 Blockers | | | | |
| Propranolol | BPH/ApoE$^{-/-}$mice | ↓ | ↓ HSPC proliferation in the BM<br>↓ GMPs in the BM<br>↓ Blood monocytes and neutrophils<br>↓ Macrophages in the lesion | [77] |
| **Second Generation: β1-Selective Blockers** | | | | |
| Metoprolol | ApoE$^{-/-}$mice | ↓ | N/R | [78] |
| | ApoE$^{-/-}$mice | ↓ | ↓ Circulating TNFα, CXCL1<br>↓ Macrophages in the lesion | [79] |
| | Subjects without symptoms | ↓ | N/R | [84] |
| | Patients with hypercholesterolemia | ↓ | N/R | [85] |
| Third Generation: Non-Selective β Blockers with Additional Properties | | | | |
| Carvedilol<br>With α1- blocking and antioxidant properties | Ldlr$^{-/-}$mice | ↓ | ↑ ABCA1 in exosomes<br>↑ Cholesterol efflux<br>↓ Macrophages in the lesion | [80] |
| | ApoE$^{-/-}$mice | ↓ | ↓ Superoxide production<br>↓ Macrophage and T cell infiltration | [81] |
| | Rabbits | ↔ | ↓ LDL oxidation<br>↑ eNOS expression<br>↑ Endothelium-dependent relaxation | [82] |
| Nipradilol<br>With NO-releasing properties | Rabbits | ↓ | ↑ eNOS<br>↑ Endothelium-dependent relaxation<br>↓ Monocyte adhesion to EC<br>↓ Monocyte/macrophage infiltration | [83] |
| Third Generation: β1-Selective Blockers with Additional Properties | | | | |
| Nebivolol<br>With NO-releasing property | Rabbits | ↓ | ↓ LDL oxidation<br>↓ Inflammatory markers<br>↑ eNOS expression<br>↑ Endothelium-dependent relaxation | [82] |

↓, decrease; ↑, increase; ↔, no effect; ABCA1, ATP binding cassette subfamily A member 1; ApoE$^{-/-}$, apolipoprotein E-deficient; BM, bone marrow; BPH, Schlager hypertensive (blood pressure high) mice; CXCL1, CXC motif chemokine ligand 1; EC, endothelial cells; eNOS, endothelial nitric oxide synthase; GMPs, granulocyte-macrophage progenitors; HSPC, hematopoietic stem and progenitor cells; LDL, low-density lipoprotein; Ldlr$^{-/-}$, LDL receptor-deficient; NO, nitric oxide; NR, not reported; and TNFα, tumornecrosis factor α.

### *7.4. Role of β2 Adrenoceptors in Atherosclerosis*

Whether β2 adrenoceptors play a role in atherosclerosis is unknown and this is worthy of investigation in the future. It has been shown that the selective blockade of β2 adrenoceptors could reduce inflammation and oxidative stress [91], suggesting that β2 adrenoceptors may be involved in atherosclerosis.

### *7.5. Role of β3 Adrenoceptors in Atherosclerosis*

#### 7.5.1. Preclinical Studies

β3 agonists inhibit atherosclerosis in mice fed with a Western-type diet in preclinical studies [92–94] (Table 3). They inhibit atherosclerosis via multiple mechanisms, e.g., (1) activating brown adipose tissue and thus increasing fat oxidation and decreasing body fat mass, (2) increasing the clearance of plasm triglyceride-rich lipoprotein (TRL), i.e., VLDL and chylomicrons, via increasing the liver uptake of VLDL core remnants and thus decreasing plasma non-HDL cholesterol, (3) increasing HDL cholesterol via promoting the

transfer of TRL particles to HDL particles, (4) increasing lipoprotein lipase lipolysis activity and thus decreasing plasma triglycerides, and (5) decreasing total cholesterol [92–95]. The resultant favorable lipid profile may explain the anti-atherosclerotic effect of β3 agonism.

**Table 3.** Effect of β3 agonism on atherosclerosis in preclinical studies.

| β3 Agonist | Animals | Effect on Atherosclerosis | Mechanisms | Reference |
|---|---|---|---|---|
| CL316,243 | E3L.CETP mice | ↓ | ↑ Energy expenditure<br>↑ Fat oxidation by activated BAT<br>↓ Total body fat mass<br>↓ Lipid droplet content in BAT<br>↓ Plasma TG, TC, and non-HDL cholesterol<br>↑ Plasma TRL clearance<br>↑ Hepatic cholesterol content<br>↑ HDL cholesterol | [92] |
| CL316,243 | E3L.CETP mice | ↓ | ↓ TC and TG<br>↑ VLDL clearance<br>↑ Liver uptake of VLDL core remnants<br>↑ Lipoprotein lipase lipolysis activity<br>↑ Transfer of VLDL to HDL cholesterol<br>↑ Plasma HDL cholesterol | [93] |
| CL316,243 | E3L.CETP mice | ↓ | ↓ Total fat mass<br>↓ Plasma TG and non-HDL cholesterol<br>↑ Plasma clearance and hepatic uptake of cholesterol-enriched TRL remnants.<br>↑ HDL cholesterol | [94] |
| CL316,243 | E3L.CETP mice | NR | ↓ Body fat masss and gonadal WAT<br>↓ Plasma TG, TC, and non-HDL cholesterol<br>↑ Clearance of TRL-like particles<br>↑ Hepatic uptake of TRL-like remnants<br>↑ Tranfer of TRL particles to HDL particles<br>↑ Plasma HDL cholesterol | [95] |

↓, decrease; ↑, increase; BAT, brown adipose tissue; E3L.CETP mice, APOE*3-Leiden crossing human cholesteryl ester transfer protein mice; HDL, high-density lipoprotein; NR, not reported; TC, total cholesterol; TG, triglyceride; TRL, triglyceride-rich lipoprotein, i.e., very-low-density lipoproteins and chylomicrons; VLDL, very-low-density lipoprotein; and WAT, white adipose tissue.

It is worth noting that β3 agonism does not affect atherosclerosis severity [94], lesion composition (smooth muscle cells, collagen, and macrophages), nor the stability of the lesion as assessed by the ratio of stable markers (collagen area or combined collagen and smooth muscle cell area) versus the unstable markers (macrophage area) [92,93].

#### 7.5.2. Clinical Studies

β3 adrenoceptors are expressed in a species-specific manner. For example, in mice, they are most highly expressed in white and brown adipose tissues, whereas in humans they are most highly expressed in the urinary bladder [54]. A β3 agonist mirabegron (Myrbetriq, extended-release tablet, Astellas Pharma) has been approved for the treatment of overactive bladder, with an approved maximum dose of 50 mg per day.

β3 agonism by mirabegron increases brown adipose tissue volume, brown adipose tissue metabolic activity, lipolysis, fat oxidation, and resting energy expenditure in humans [54,96,97]. It also increases HDL cholesterol, apolipoprotein A1 (ApoA1), and ApoE [96]. These results suggest that β3 agonism may inhibit atherosclerosis in humans.

It is worth noting that high doses of mirabegron have unfavorable cardiovascular effects. Mirabegron increased the heart rate, blood pressure, and rate-pressure product (an indicator of myocardial oxygen consumption) in clinical trials at doses higher than the approved maximum therapeutic dose of 50 mg per day [54,96–98]. In addition, mirabegron caused QT prolongation in women but not men at the supratherapeutic dose of 200 mg per day [98]. These cardiovascular side effects were not significant at the therapeutic 50 mg

dose [54,98]. The reason for the high-dose mirabegron-induced cardiovascular stimulation is unknown. It is possible that the high dose of mirabegron is taken up by sympathetic nerve terminals which causes the release of norepinephrine and activation of β1 adrenoceptors in cardiomyocytes [96]. Therefore, a low dose of mirabegron should be used in future clinical trials investigating the potential anti-atherosclerotic effect of β3 agonism.

## 8. Renal Denervation and Atherosclerosis

Renal denervation is used to lower the blood pressure of hypertensive patients via the inhibition of sympathetic activity [99–101]. It may have beneficial effects in other indications beyond hypertension, such as renal failure [102,103] and atrial fibrillation [104]. Here, we summarize the recent studies investigating the effect of renal denervation on atherosclerosis in preclinical and clinical studies.

### *8.1. Preclinical Studies*

Three preclinical studies have shown that renal denervation decreased atherosclerosis independent of blood pressure in ApoE$^{-/-}$mice fed with a high-fat diet [105–107]. This may be mediated by a decrease in monoamine oxidase (MAO). Norepinephrine is metabolized by MAO to produce oxidants including aldehyde and hydrogen peroxide (Figure 6). High-fat diet feeding in mice increases MAO activity [105,108], which impairs mitochondrial homeostasis and increases reactive oxygen species (ROS) production and nuclear factor kappa B (NF-κB) activation [105]. Renal denervation decreased aortic MAO-A and inflammation, and decreased macrophage accumulation in the lesion [105]. The anti-inflammatory effect of renal denervation in high-fat diet-fed mice has been confirmed by another two studies [106,107] (Table 4).

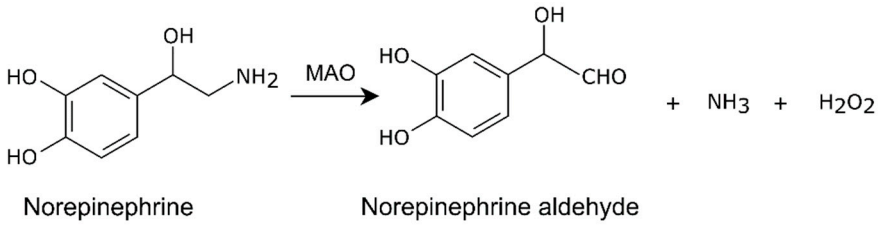


**Figure 6.** Production of oxidants by norepinephrine metabolism.

In contrast, two preclinical studies found that renal denervation increased atherosclerosis in mice [109] and minipigs [110] (Table 4). The pro-atherosclerotic effect of renal denervation is associated with an increase in matrix metalloproteinase-2 (MMP-2, a pro-atherosclerotic marker) [109,111–113] and endothelin-1 [110].

Activated MMP-2 is an alternative to the endothelin converting enzyme as it can convert the big inactive precursor big endothelin-1 to active endothelin-1 [114,115]. Endothelin activates NF-κB in human endothelial cells [116] and increases NADPH oxidase and superoxide production in pulmonary arteries [117]. Renal denervation increased MMP-2 [109] and endothelin-1 protein and its receptors [110], which was accompanied by the activation of NF-κB and NADPH oxidase pathways [110]. The renal denervation-induced increase in oxidative stress was indicated by an increase in 4-hydroxynonenal [110], a marker of oxidative stress and atherosclerosis [118]. In addition, renal denervation may inhibit the endothelial nitric oxide synthase–nitric oxide (eNOS-NO) pathway which may promote atherosclerosis [110].

### *8.2. Clinical Studies*

It has been shown that renal denervation in humans, a blood-pressure-lowering therapy [119–121], might slightly increase the occurrence of renal artery stenosis, with an occurrence rate of 0.3–2.2%, although some studies reported a higher rate of more than 10% [122,123].

In a clinical study with a small sample size ($n$ = 39), renal denervation did not affect atherosclerosis after 12 months in those with resistant hypertension (Table 4). However, the longer-term effect of renal denervation on atherosclerosis in humans is not available and needs to be investigated in the future. Careful consideration should be given when performing renal denervation in patients with severe atherosclerosis or stenosis [124–128]. It has been reported that renal denervation increases MMP-2 in both animals [109] and humans [129], and an increase in MMP-2 may adversely affect the stability of severe atherosclerosis [130].

**Table 4.** Effect of renal denervation on atherosclerosis in preclinical and clinical studies.

| Patients/Animals | Effect on Atherosclerosis | Mechanisms | Reference |
|---|---|---|---|
| Preclinical Studies | | | |
| ApoE$^{-/-}$mice<br>HFD for 20 weeks | ↓ | ↓ MAO-A<br>↓ CCL2, ICAM-1<br>↓ Macrophage<br>↓ ROS<br>↓ NF-κB | [105] |
| ApoE$^{-/-}$mice<br>HFD for 6–12 weeks | ↓ | ↓ TNFα, IL-Iβ, etc<br>↓ Circulating neutrophils<br>↓ Circulating monocytes | [106] |
| ApoE$^{-/-}$mice<br>HFD for 10 weeks | ↓ | ↑ VSMC<br>↓ CCL2 and 8-isoprostane | [107] |
| ApoE$^{-/-}$mice<br>Angiotensin II fusion | ↑ | ↑ MMP-2 | [109] |
| Minipigs<br>HFD for 6 months | ↑ | ↑ ET-1<br>↑ ET-1 A and Breceptors<br>↑ NOX2<br>↑ NF-κB<br>↑ 4-hydroxynonenal<br>↓ eNOS phosphorylation<br>↓ NO | [110] |
| Clinical studies | | | |
| 39 patients with rHTN | ↔ | NR | [131] |

↔, no effect; ↑, increase; ↓, decrease; ApoE$^{-/-}$, apolipoprotein E-deficient; CCL2, chemokine ligand 2; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; HFD, high fat diet; ICAM, intercellular adhesion molecule; IL, interleukin; MAO, monoamine oxidase; MMP-2, matrix metalloproteinase-2; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOX, NADPH oxidase; NR, not reported; rHTN, resistant hypertension; ROS, reactive oxygen species; TNFα, tumor necrosis factor α; and VSMCs, vascular smooth muscle cells.

## 9. Artery–Brain Circuit and Atherosclerosis

### *9.1. Establishment of the Artery–Brain Circuit in Mice*

A significant development in vascular sympathetic innervation is the recent establishment of the artery–brain circuit in the mouse abdominal aorta by Mohanta et al. [11]. In the artery–brain circuit sensor pathway, signals from the sensory afferent neurons, which innervate the abdominal aorta, pass through the dorsal root ganglia, enter the spinal cord via the spinal cord dorsal horn, and then transmit to the brain stem medulla oblongata. In the artery–brain circuit effector pathway, sympathetic signals from the hypothalamic and brainstem nuclei pass the spinal cord and then the coeliac ganglia and finally reach the aortic adventitia; in addition, parasympathetic signals from the medulla oblongata can pass on to the coeliac ganglia via the vagal nerve [11].

The artery–brain circuit plays an important role in regulating vascular inflammation. It has been shown that coeliac ganglionectomy, which was confirmed by a decrease in norepinephrine content and the density of tyrosine hydroxylase-positive sympathetic nerves in the aorta, decreased the number and size of artery tertiary lymphoid organs (ATLOs,

structures in the adventitia where infiltrated immune cells aggregate), and attenuated T and B cell vascular infiltration in aged ApoE$^{-/-}$mice [11].

### 9.2. Ganglionectomy and Atherosclerosis

Disruption of the artery–brain circuit by coeliac ganglionectomy decreased the atherosclerotic plaque size in the aortic arch and abdominal aorta of aged ApoE$^{-/-}$mice as assessed by ultrasound imaging [11]. The anti-atherosclerotic effect of coeliac ganglionectomy was associated with the decreased vascular infiltration of immune cells [11]. These results suggest that the artery–brain circuit may promote vascular inflammation and atherosclerosis.

It is worth noting that contradicting results exist. A study by Murphy et al., conducted in the 1950s, showed that removal of L1 to L4 ganglia increased atherosclerosis in the abdominal aorta and femoral arteries of rabbits fed a high-cholesterol diet [132]. To assure adequate denervation, Murphy et al. performed "a peri-aortic stripping of all adventitia" of the infrarenal aorta in addition to the removal of the ganglia. Whether this additional procedure explains the observed inconsistency needs to be investigated in the future.

## 10. Sympathetic Nervous System and Peripheral Artery Disease (PAD)

PAD, also known as atherosclerotic occlusive disease of the lower extremities, affects more than 200 million people worldwide [133]. Patients with PAD display cardiac autonomic dysfunction [134], increased sympathetic nerve activity, and an augmented blood pressure response to exercise [135,136]. The increase in sympathetic nerve activity in PAD is associated with an increase in sensory nerve receptors (e.g., receptor potential vanilloid type 1, purinergic P2X purinoceptor 3, and acid-sensing ion channel subtype 3) [137]. Cardiac autonomic dysfunction has also been shown to predict a higher risk for cardiovascular disease events in atherosclerosis-prone diabetic patients [138,139]. Whether the sympathetic nervous system plays a role in the progression of atherosclerosis underlying PAD needs to be investigated in the future.

## 11. Concluding Remarks

Major arteries and arterioles are innervated by sympathetic nerves and all types of adrenoceptors (α1, α2, β1, β2, and β3) are expressed in arterial blood vessels. α1 blockers inhibit atherosclerosis; however, their use increases the risk of heart failure. Therefore, whether α1 blockers provide a long-term cardiovascular benefit needs to be investigated in the future. α2 stimulation inhibits sympathetic activity and the non-specific α2 agonist moxonidine inhibits atherosclerosis in ApoE$^{-/-}$mice. The definitive role of the α2 adrenoceptors in atherosclerosis needs to be investigated using selective α2 agonists and confirmed in humans.

β blockers (selective and non-selective β1 blockers) are currently not recommended for treating atherosclerosis due to adverse effects on lipoprotein levels, such as increasing VLDL and decreasing HDL cholesterol. However, many recent preclinical studies have shown that β blockers can attenuate atherosclerosis progression without adverse effects on plasma total cholesterol, triglycerides, or HDL cholesterol. Two randomized controlled trials have shown that β blockers reduce the progression of atherosclerosis in humans even in the presence of concomitant lipid-lowering therapy. In addition, many newer generations of β blockers have additional favorable properties, including promoting cholesterol efflux, inhibiting oxidative stress, and improving endothelial function. Therefore, more randomized controlled trials are needed to establish the use of β blockers for atherosclerosis inhibition and cardiovascular risk reduction. In future trials, low-dose and controlled-release formulations of β blockers and newer generations of β blockers are worthy of consideration.

β3 agonism is gaining interest as a potential strategy to inhibit atherosclerosis. Preclinical studies show consistent results on the anti-atherosclerosis effect of β3 agonism, which is mediated by activating brown adipose tissue metabolism and increasing fat oxidation. However, the effect of β3 agonism on atherosclerosis in humans has not been investigated.

Given that higher doses of β3 agonists could increase blood pressure and heart rate and increase the risk of QT prolongation, it is worthy of consideration to use low doses of β3 agonists or controlled release formations in future clinical trials.

The effects of renal denervation on atherosclerosis are inconsistent in preclinical studies. Whether renal denervation inhibits atherosclerosis in humans needs to be established in the future.

**Author Contributions:** Conceptualization, Y.W.; data curation, Y.W., J.A., M.C.M. and M.A.M.; writing—original draft preparation Y.W.; writing—review and editing, Y.W., J.A., M.C.M., M.A.M., E.O., C.G.S., G.R.D. and K.M.D.; visualization, Y.W.; funding acquisition, Y.W. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the National Health and Medical Research Council of Australia, grant number 1062671.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** We thank Na-Qiong Wu and Xiulin Zhang for their critical review of the manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

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