

# Renin–angiotensin–aldosterone system in insulin resistance and metabolic syndrome

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## ABSTRACT

Obesity and its consequent complications such as hypertension and metabolic syndrome are increasing in incidence in almost all countries. Insulin resistance is common in obesity. Renin–angiotensin system (RAS) is an important target in the treatment of hypertension and drugs that act on RAS improve insulin resistance and decrease the incidence of type 2 diabetes mellitus, explaining the close association between hypertension and type 2 diabetes mellitus. RAS influences food intake by modulating the hypothalamic expression of neuropeptide Y and orexins via AMPK dephosphorylation. Estrogen reduces appetite by its action on the brain in a way similar to leptin, an anorexigenic action that seems to be mediated via hypothalamic pro-opiomelanocortin (POMC) neurons in the arcuate nucleus and synaptic plasticity in the arcuate nucleus similar to leptin. Estrogen stimulates lipoxin A<sub>4</sub>, a potent vasodilator and platelet anti-aggregator. Since both RAS and estrogen act on the hypothalamic neuropeptides and regulate food intake and obesity, it is likely that RAS modulates LXA<sub>4</sub> synthesis. Thus, it is proposed that Angiotensin-II receptor blockers and angiotensin-converting enzymes and angiotensin-II antagonists may have the ability to augment LXA<sub>4</sub> synthesis and thus bring about their beneficial actions.

**Key words:** renin, angiotensin, lipoxin A<sub>4</sub>, oestrogen, free radicals, hypertension, diabetes mellitus, metabolic syndrome, food intake

## INTRODUCTION

Obesity is now assuming epidemic proportions worldwide. Elevated arterial pressure is a frequent complication of excess body weight, and both obesity and hypertension are components of insulin-resistance syndrome [1,2]. Many obese hypertensive patients tend to develop type-2 diabetes mellitus, which further increases their cardiovascular risk. While lifestyle modification is the key to weight and blood pressure reduction, pharmacological intervention remains essential to lowering blood pressure to target levels in obese patients with hypertension. Antihypertensive drugs such as thiazide diuretics and  $\beta$ -blockers adversely affect glucose metabolism and increase the risk of developing type-2 diabetes [3-6], though this has been disputed [7-11]. On the other hand, drugs that interfere with the renin–angiotensin system (RAS) improve insulin sensitivity, produce a

significant decline of albuminuria, induce a drop of the pathological glomerular hyperfiltration, and reduce the incidence of new-onset diabetes [12-17]. Therefore, the initial selection of antihypertensive therapy for obese patients could have a significant influence on their overall cardiovascular risk. In this context, the beneficial actions of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in the prevention or postponement of the development of type 2 diabetes mellitus in hypertensives who are at high risk of development of type 2 diabetes mellitus needs a closer look [18, 19].

**FREE RADICALS,  
NITRIC OXIDE (NO),  
EICOSANOIDS, PRO- AND  
ANTI-INFLAMMATORY  
CYTOKINES, AND  
LONG-CHAIN  
POLYUNSATURATED FATTY**

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## ACIDS (PUFAS) IN HYPERTENSION AND TYPE 2 DIABETES MELLITUS

There is a close association between hypertension and type 2 diabetes mellitus that could be attributed to the involvement of free radicals, nitric oxide (NO), eicosanoids, pro- and anti-inflammatory cytokines, long-chain polyunsaturated fatty acids (PUFAs) and their metabolites, folic acid, and vitamin C in the pathogenesis of both hypertension and type 2 diabetes mellitus. For example, under physiological conditions, a balance is maintained between endothelial vasoconstrictors and vasodilators such that normal blood pressure is maintained. When this balance is altered more in favor of vasoconstrictors and/or when the concentrations of vasodilators are reduced, hypertension develops. One mechanism by which endothelium-dependent vasodilatation is impaired is due to an increase in the oxidative stress that inactivates NO and PGI<sub>2</sub> (prostacyclin). Polymorphonuclear leucocytes of patients with uncontrolled essential hypertension produce significantly large amounts of superoxide anion and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), and lipid peroxides, indicating that an increase in oxidative stress occurs in hypertension<sup>[20-23]</sup>. In addition, a decrease in the levels of superoxide dismutase (SOD), catalase, glutathione peroxidase, and vitamin E in the RBC membranes of uncontrolled hypertensives was noted. These biochemical abnormalities revert to normal after the control of hypertension. Thus, decreased NO bioavailability and increased superoxide anion generation due to enhanced NAD(P)H oxidase activity could be responsible for oxidative stress seen in hypertension. These evidences coupled with the observation that a graded positive relationship exists between blood pressure and levels of intercellular adhesion molecule-1 (ICAM-1) as well as IL-6 was in healthy men<sup>[24]</sup> suggests that low-grade systemic inflammation occurs in hypertension.

In a similar fashion, plasma levels of C-reactive protein (CRP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-6 (IL-6) are elevated in subjects with type 2 diabetes, indicating the existence of low-grade systemic inflammation in diabetics too<sup>[25]</sup>. Dietary glycemic load is significantly and positively associated with plasma CRP (26), suggesting that hyperglycemia induces inflammation. Since low-grade systemic inflammation occurs both in hypertension and type 2 diabetes mellitus, it is not surprising that blood pressure progression is a strong and independent predictor of occurrence of type 2 diabetes in hypertensives. In view of the overlap biochemical abnormalities in obesity, type 2 diabetes, hypertension, and insulin resistance such as cytokines, adipokines, reactive oxygen species, antioxidants, and NO, it is reasonable to suggest that low-grade systemic inflammation is the underlying pathophysiological process in them.

## ANGIOTENSIN-II IS PRO-INFLAMMATORY IN NATURE

Several studies indicated that ACE inhibitor therapy reduces the development of type 2 diabetes in persons with essential hypertension, a population with a high prevalence of insulin resistance. ACE inhibitor therapy has been shown to improve surrogates of cardiovascular disease (e.g., vascular compliance, endothelial-derived nitric oxide production, vascular relaxation and plasma markers of inflammation, oxidative stress, and thrombosis) and reduce cardiovascular disease, renal disease progression, and stroke<sup>[27]</sup>. These anti-inflammatory actions of ACE inhibitors and angiotensin-II receptor blockers may explain their possible beneficial action in the prevention of development of type 2 diabetes mellitus in those who were given these drugs for the management of hypertension. This implies that enhanced circulating levels of renin, angiotensin-II, and aldosterone as a result of overactive renin–angiotensin–aldosterone system could predispose or initiate the development of insulin resistance, type 2 diabetes mellitus, and metabolic syndrome in subjects with hypertension. This is supported by the observation that angiotensin-II is pro-inflammatory in nature and angiotensin-II receptor blockers and angiotensin-II antagonists have anti-inflammatory actions<sup>[28,29]</sup>. Since both hypertension and type 2 diabetes mellitus are low-grade systemic inflammatory conditions, this amply supports the involvement of renin–angiotensin system in the pathobiology of hypertension and type 2 diabetes mellitus.

## RAS AND FOOD INTAKE

Since obesity is common in subjects with insulin resistance, hypertension, and type 2 diabetes mellitus, and obesity results from increased intake of energy-dense food, it is reasonable to propose that, in all probability, renin–angiotensin–aldosterone system (RAS) and/or angiotensin-II, the principal hormone of the RAS, may have a role in food intake<sup>[28]</sup>. Sasaki et al<sup>[29]</sup> noted that consumption of total lipids, cholesterol, and unsaturated free fatty acids was higher in MM/MT of *AGT* (angiotensinogen) Met235Thr than TT polymorphism. However, it was observed that the *AGT* polymorphism (rs7079), and the *ACE* I/D were not associated with food preferences. In contrast, it was noted that the *ADRB3* Trp64 (adrenergic  $\beta$ 3 receptor = *ADRB3* gene) polymorphisms tended to show high-energy intake and preferences to protein and lipids including fatty acids and cholesterol. These studies led to the conclusion that *AGT* Met235Thr polymorphism was significantly associated with higher caloric intake due to total fats and carbohydrate consumption, emphasizing the

importance of angiotensin-II and adrenergic  $\beta 3$  receptor in higher caloric intake due to total fats and carbohydrate consumption.

The regulatory role of RAS in the control of water and sodium intake is well documented by its action on kidney and brain that may also explain the role of central renin–angiotensin system in the pathogenesis of hypertension [30–33]. It was reported that intracerebroventricular (ICV) infusion of the angiotensin antagonist [Sar1,Thr8]-AII, effectively lowered the blood pressure in normotensive rats. These and other studies led to the conclusion that perturbations of the endogenous brain–angiotensin system are effective at rapidly influencing both cardiovascular and body fluid homeostasis [34]. Some of these actions of Ang-II seem to be mediated by its stimulatory action on the release of vasopressin [35] and its action on the paraventricular nucleus of the hypothalamus [36], a center that is known to be an important site of integration for sympathetic outflow. When renal sympathetic nerve discharge (RSND), arterial blood pressure (AP), and heart rate (HR) were measured in response to administration of ANG II and N(G)-monomethyl-L-arginine (L-NMMA) into the PVN, it was noted that Ang-II (0.05, 0.5, and 1.0 nmol) into the PVN increased RSND, AP, and HR in a dose-dependent manner. These responses were significantly enhanced by prior microinjection of L-NMMA and administration of antisense to neuronal NO synthase within the PVN and were blocked by losartan, an Ang-II type 1 receptor antagonist. Conversely, overexpression of neuronal nitric oxide synthase (NOS) within the PVN with adenoviral gene transfer significantly attenuated Ang-II responses, whereas Ang-II (1 nmol) when injected into the PVN induced an increase in NO release. These results indicate that Ang-II type 1 receptors within the PVN mediate an excitatory effect on RSND, AP, and HR, while NO in the PVN, which can be induced by ANG II stimulation, in turn inhibits the Ang-II-mediated increase in sympathetic nerve activity. This negative feedback mechanism within the PVN may play an important role in maintaining the overall balance and tone of sympathetic outflow [37–39] and suggests that Ang-II and NO interact with each other and regulate water and sodium intake and blood pressure by their central action, an action that is predominantly mediated by Ang-type 1 (AT(1)) receptor. Subsequent studies revealed that Ang-II acts through G protein-coupled receptors of two pharmacological classes, AT(1) and AT(2), wherein AT(1) receptors, expressed in brain and peripheral tissues, mediate blood pressure homeostasis and regulation of drinking and water balance. In rodents, two highly homologous AT(1) receptor isoforms, termed AT(1A) and AT(1B) receptors, expressed in major forebrain cardiovascular and fluid regulatory centers, with AT(1A) regulating the blood pressure in response to centrally administered angiotensin II while the drinking response is mediated by AT(1B) receptors [40].

## RAS AND BODY WEIGHT

Furthermore, Ang-II decreases body weight by its ability to stimulate sympathetic neurotransmission to interscapular brown adipose tissue (ISBAT), which is characterized by enhanced release of norepinephrine (NE) from ISBAT sympathetic nerve terminals. Increased sympathetic neurotransmission to ISBAT may contribute to Ang-II-regulation of body weight [41] that suggests that Ang-II regulates body weight through mechanisms related to increased peripheral metabolism and independent of elevations in blood pressure [42]. This is supported by the observation that angiotensinogen-deficient mice exhibit impairment of diet-induced weight gain with alteration in adipose tissue development and increased locomotor activity [43], have increased energy expenditure, with reduced fat mass, and improved glucose clearance [44, 45], events that are in support of the beneficial actions of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in the prevention or postponement of the development of type 2 diabetes mellitus in hypertensives [18, 19].

Central AT(1) receptor signaling plays a homeostatic role in the regulation of food intake by maintaining gene expression of corticotropin-releasing hormone in hypothalamus [46]. Ang-II acts in the brain to promote negative energy balance by altering the hypothalamic circuits regulating energy balance that include increased uncoupling protein-1 and  $\beta(3)$ -adrenergic receptor expression in brown adipose tissue and  $\beta 3$ -adrenergic receptor expression in white adipose tissue, suggesting enhanced sympathetic activation and thermogenesis; decrease food intake, increase in energy expenditure [47], and finally Ang II type-1a receptor-dependent Ang-II signaling reduces food intake by suppressing the hypothalamic expression of neuropeptide Y and orexins via AMPK dephosphorylation [48].

## RAS, ESTROGEN, AND LIPOXIN A4

In this context, it is noteworthy that ovariectomized (OVX) female rats treated with estradiol benzoate (EB) had a 30–40% reduction in the levels of AT-I receptor mRNA in pituitary and HTS (hypothalamic-thalamic-septa) tissue samples as compared to OVX, control animals. In the pituitary, the mRNA levels for angiotensinogen (AGT) were increased by 45% following estrogen administration. In addition, a reduction in [<sup>125</sup>I]-AngII binding to AT-I receptors in the pituitary and the subfornical organ following estrogen treatment was noted. These results suggest that estrogen modulates the pituitary and central RAS through a coordinate regulation of the angiotensin receptors and the levels of newly synthesized Ang-II [49], which may explain sex-dependent changes in the response

of male and females to Ang-II antagonists and Ang-II receptor blockers.

Estrogen reduces appetite by its action in the brain in a way similar to leptin<sup>[50]</sup>. But, the clinical use of estrogen to reduce body weight and appetite limited due to the severity of its side effects, especially increased incidence of cancer after its use. Anorexigenic effects of estrogen are strongly linked to its action on hypothalamic pro-opiomelanocortin (POMC) neurons in the arcuate nucleus<sup>[51]</sup>. Estrogen induces rapid synaptic plasticity in the arcuate nucleus, an effect similar to those of leptin<sup>[52]</sup>.

Estrogen augments synthesis of lipoxin A<sub>4</sub> (LXA<sub>4</sub>), a potent anti-inflammatory bioactive lipid formed from arachidonic acid (AA). Lipoxins are a group of nonclassic eicosanoids that possess potent anti-inflammatory and proresolution properties<sup>[53-58]</sup>. Endometrium contains 15-LOX-2, an enzyme necessary for lipoxin biosynthesis. LXA<sub>4</sub> showed robust estrogenic activity through its capacity to alter estrogen receptor transcriptional activity, as well as expression of estrogen-regulated genes and proliferation of human endometrial epithelial cells. The actions of LXA<sub>4</sub> are exclusively mediated through estrogen receptor and closely mimic those of the potent estrogen, 17β-estradiol. LXA<sub>4</sub> exhibited estrogenic activity in vivo, increasing uterine wet weight and modulating 17β-estradiol regulated gene expression<sup>[59]</sup>. These studies<sup>[59-62]</sup> suggest that LXA<sub>4</sub> mediates anti-inflammatory actions of estrogen. Since LXA<sub>4</sub> induces the production and release of eNO<sup>[63-65]</sup>, this implies that estrogen induced LXA<sub>4</sub> synthesis, which, in turn, enhances eNO generation. The broader implication of the action of estrogen on LXA<sub>4</sub> synthesis is that several beneficial actions of estrogen could be mediated by LXA<sub>4</sub>. Some of these actions could include its (estrogen) anti-inflammatory, antiatherosclerotic, antihypertensive, vasodilator, and anti-preeclamptic actions. In addition, exercise that is beneficial in the prevention and management of obesity, type 2 diabetes mellitus, hypertension, and metabolic syndrome also augments LXA<sub>4</sub> formation<sup>[66]</sup>. This implies that LXA<sub>4</sub> may function as an endogenous antidiabetic and antihypertensive molecule<sup>[67]</sup> and may function as a physiological antagonist of Ang-II.

It is evident from the preceding discussion that RAS and Ang-II, in particular, does influence food intake, energy expenditure, and development of obesity and type 2 diabetes mellitus apart from its influence on water, salt balance, and blood pressure (Figure 1).

In the light of these facts, it would be interesting to study plasma levels of ghrelin, cholecystokinin, GLP-1 (glucagon-like peptide-1) and other incretins, LXA<sub>4</sub>, and vagal tone and correlate them to changes in body weight,

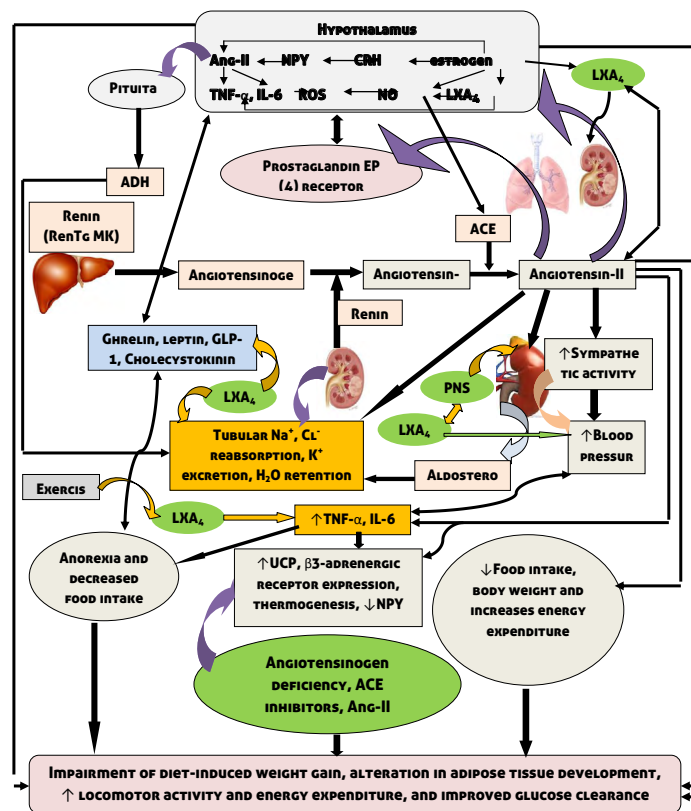
food intake, insulin resistance, and glucose tolerance in the transgenic mouse model overexpressing renin in the liver (RenTgMK). It is suggested that RAS will have a modulatory action on LXA<sub>4</sub> synthesis. It is predicted that angiotensin-II may suppress LXA<sub>4</sub> formation and thus bring about its pro-inflammatory actions, while Ang-II and Ang-II receptor antagonists promote LXA<sub>4</sub> formation. This implies that plasma levels of LXA<sub>4</sub> could be used as a marker of the actions of Ang-II and Ang-II receptor antagonists: plasma LXA<sub>4</sub> levels would increase when the dose and action of Ang-II and Ang-II receptor antagonists are optimal. Thus, there could occur an integrated and coordinated interaction(s) among RAS, estrogen, ghrelin, cholecystokinin, GLP-1 (glucagon-like peptide-1), and other incretins, hypothalamic neurotransmitters and neuropeptides, LXA<sub>4</sub>, and vagal tone that ultimately determines appetite, food intake, autonomic nervous system tone and function, development of hypertension, obesity, metabolic syndrome, and type 2 diabetes mellitus (Figure 1). A better understanding of such interaction(s) could lead to more targeted therapeutic and preventive strategies for obesity, hypertension, and metabolic syndrome.

## Conflict of Interest

None declared.

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**Figure 1:** Scheme showing the involvement of renin-angiotensin-aldosterone system on food intake, energy expenditure, water, salt balance and blood pressure. Angiotensin is a peptide hormone that causes vasoconstriction and a subsequent increase in blood pressure. It is part of the renin–angiotensin system, which is a major target for drugs that lower blood pressure. Angiotensin stimulates the release of aldosterone from the adrenal cortex that promotes sodium retention in the distal nephron, in the kidney, which drives blood pressure up. Angiotensin, an oligopeptide hormone, derived from the precursor molecule angiotensinogen, a serum globulin produced in the liver. Human angiotensinogen is 452 amino acids long and is converted to angiotensin-I by the action of renin that is produced by the kidneys in response to renal sympathetic activity, decreased intrarenal blood pressure at the juxtaglomerular cells, or decreased delivery of Na<sup>+</sup> and Cl<sup>-</sup> to the macula densa. If less Na<sup>+</sup> is sensed by the macula densa, renin release by juxtaglomerular cells is increased. Angiotensin-I has no biological activity and exists solely as a precursor to angiotensin II. Angiotensin-I is converted to angiotensin-II (Ang-II) by the enzyme angiotensin-converting enzyme (ACE), primarily through ACE within the kidney. ACE found in other tissues of the body such as lungs, but activation here promotes no vasoconstriction, as the level of angiotensin-II is below physiological levels of action. Angiotensin-II acts as an endocrine, autocrine/paracrine, and intracrine hormone. ACE inhibitor drugs decrease the rate of Ang-II production. Angiotensin II increases blood pressure. ACE inhibitor drugs are major drugs against hypertension. The action of Ang-II itself is targeted by angiotensin II receptor antagonists, which directly block angiotensin-II AT<sub>1</sub> receptors. Nitric oxide is a potent inhibitor of ACE. Ang-II also acts on the pituitary gland to induce the release of ADH (antidiuretic hormone) that enhances water absorption in the collecting ducts of the kidney. It is known that Ang-II has proinflammatory actions, enhances the production of IL-6 and TNF-α and augments free radical generation reactive oxygen species, ROS. Ang-II does influence food intake and energy expenditure apart from its influence on water, salt balance, and blood pressure. Ang-II receptors are present in the brain and especially in the hypothalamus. Ang-II acts in the brain to promote negative energy balance by altering the hypothalamic circuits regulating energy balance that include increased uncoupling protein-1 and β(3)-adrenergic receptor expression in brown adipose tissue and β3-adrenergic receptor expression in white adipose tissue, suggesting enhanced sympathetic activation and thermogenesis; decrease food intake, increase in energy expenditure, and finally Ang II type-1a receptor-dependent Ang-II signaling reduces food intake by suppressing the hypothalamic expression of neuropeptide Y and orexins via AMPK dephosphorylation. Ang-II regulates body weight through mechanisms related to increased peripheral metabolism and independent of elevations in blood pressure. In addition and in a paradoxical fashion, angiotensinogen-deficient mice exhibit impairment of diet-induced weight gain with alteration in adipose tissue development and increased locomotor activity, have increased energy expenditure, with reduced fat mass and improved glucose clearance, events that explain the beneficial actions of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in the prevention or postponement of the development of obesity, type 2 diabetes mellitus and metabolic syndrome in hypertensives. In a transgenic mouse model overexpressing renin in the liver (RenTgMK) led to constitutively elevated plasma angiotensin II (four- to sixfold increase vs. wild type). RenTgMK mice developed glucose intolerance despite low levels of adiposity and low plasma insulin levels. The transgenics also had lower plasma triglyceride levels. Glucose intolerance in RenTgMK transgenic mice fed a low-fat diet was comparable to that observed in high fat-fed wild type mice, suggesting that overexpression of renin and associated hyperangiotensinemia impair glucose tolerance in a diet-dependent manner lending support to the concept that the involvement of renin–angiotensin system (RAS) in the pathogenesis of diabetes and insulin resistance is independent of changes in fat mass. It is noteworthy that estrogen stimulates the production of lipoxin A<sub>4</sub> (LXA<sub>4</sub>), a potent vasodilator, platelet antiaggregator and anti-inflammatory molecule formed from arachidonic acid (AA, 20:4 n-6). LXA<sub>4</sub> suppresses the production of IL-6 and TNF-α and could antagonize the pro-inflammatory and pro-hypertensive actions of angiotensin-II. High-fat diet induced apoptosis of hypothalamic neurons could be blocked by the presence of appropriate amounts of LXA<sub>4</sub> and it (LXA<sub>4</sub>) could also suppress the formation of ROS in the hypothalamus. LXA<sub>4</sub> induces the production of endothelial nitric oxide (eNO), which, in turn, neutralizes ROS. NO is a vasodilator, possesses antihypertensive action and acts as platelet antiaggregator and serves as a neurotransmitter. Both NO and LXA<sub>4</sub> may regulate hypothalamic neurotransmitters and other peptides such as serotonin, dopamine, NPY, CRH, and melanocortins. Acetylcholine, the principal neurotransmitter of vagus, stimulates NO generation and possibly, LXA<sub>4</sub>, and it (acetylcholine) has potent anti-inflammatory actions. The antihypertensive action of renal sympathetic denervation for the treatment of resistant hypertension could be attributed at least, in part, to concomitant increase in the tone of parasympathetic nervous system (increase in vagal tone) since normally a balance is maintained between sympathetic and parasympathetic nervous systems, which leads to increase in the production of acetylcholine and consequent increase in NO and LXA<sub>4</sub> generation.

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