Modulation of glucose metabolism by the renin-angiotensin-aldosterone system

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Am J Physiol Endocrinol Metab 308: E435–E449, 2015. First published January 6, 2015; doi:10.1152/ajpendo.00391.2014.—The renin-angiotensin-aldosterone system (RAAS) is an enzymatic cascade functioning in a paracrine and autocrine fashion. In animals and humans, RAAS intrinsic to tissues modulates food intake, metabolic rate, adiposity, insulin sensitivity, and insulin secretion. A large array of observations shows that dysregulation of RAAS in the metabolic syndrome favors type 2 diabetes. Remarkably, angiotensin-converting enzyme inhibitors, suppressing the synthesis of angiotensin II (ANG II), and angiotensin receptor blockers, targeting the ANG II type 1 receptor, prevent diabetes in patients with hypertensive or ischemic cardiopathy. These drugs interrupt the negative feedback loop of ANG II on the RAAS cascade, which results in increased production of angiotensins. In addition, they change the tissue expression of RAAS components. Therefore, the concept of a dual axis of RAAS regarding glucose homeostasis has emerged. The RAAS deleterious axis increases the production of inflammatory cytokines and raises oxidative stress, exacerbating the insulin resistance and decreasing insulin secretion. The beneficial axis promotes adipogenesis, blocks the production of inflammatory cytokines, and lowers oxidative stress, thereby improving insulin sensitivity and secretion. Currently, drugs targeting RAAS are not given for the purpose of preventing diabetes in humans. However, we anticipate that in the near future the discovery of novel means to modulate the RAAS beneficial axis will result in a decisive therapeutic breakthrough.

renin-angiotensin-aldosterone system; insulin resistance; insulin target tissues; white adipose tissue; obesity

the metabolic syndrome is a constellation of disorders that includes hypertension, dyslipidemia, hyperglycemia, and obesity, predisposing to diabetes and ultimately to an increased risk of cardiovascular death (6). The metabolic syndrome is defined in humans by the presence of at least three among the five following criteria: systolic blood pressure ≥130 and/or diastolic blood pressure ≥80 mmHg, fasting glycemia ≥100 mg/dl, plasma triglyceride levels ≥1.7 mmol/l, plasma levels of high-density lipoprotein cholesterol <1.0 or 1.3 mmol/l in men and women, respectively, and elevated waist circumference, the values of which depend on sex and ethnic origin (6). The renin-angiotensin-aldosterone system (RAAS) functions as a hormonal system that is able to act directly in many tissues in an autocrine and paracrine way (140). White adipose tissue (WAT) plays a central role in the pathophysiology of the metabolic syndrome because it accounts for the increased oxidative stress and the low-grade inflammatory state observed in obesity, which in turn favors insulin resistance (151). Insulin resistance is the cornerstone of the metabolic syndrome (148), wherein RAAS is clearly involved (112, 146). A large body of evidence shows that RAAS blockade improves glucose homeostasis and prevents diabetes in patients suffering from the metabolic syndrome (7, 13, 65). Many efforts have been made to understand the processes of these beneficial effects (38, 55, 75, 82, 112, 121, 146, 179). It appears that modulation of RAAS components leads to changes in body WAT content and function. For example, RAAS intrinsic to the WAT of lean subjects regulates adipogenesis, triglyceride storage, or release. In contrast, in obesity RAAS increases oxidative stress and inflammation in WAT. Actually, RAAS components are not only present in WAT but also produced in the skeletal muscle, the liver, and the pancreatic islets, where they modulate insulin production from β-cells. In these key tissues for blood glucose control, RAAS governs a dual axis with opposing effects on glucose homeostasis. The angiotensin (ANG) II receptor type 1 (AT1R) and aldosterone favor hyperglycemia and generate an increased

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diabetes risk. On the flip side, the ANG II receptor type 2 (AT2R) and Mas receptor tend to lower glycemia and protect against the risk of developing diabetes.

In this review we describe the modulation of glucose metabolism by RAAS. In this context, we address the pathophysiological role of RAAS intrinsic to insulin target tissues and pancreatic islets, focusing more particularly on WAT. Finally, we point to new areas of therapeutic importance. Of note, the regulation of tissue blood supply and blood pressure by RAAS and insulin will not be discussed. Readers are invited to recent reviews on this issue (28, 34, 78, 127).

The Renin-Angiotensin-Aldosterone System

The RAAS is an enzymatic cascade (Fig. 1A). The rate-limiting step of RAAS is the synthesis of ANG I through cutting off a decapeptide at the NH2-terminal part of angiotensinogen (AGT) by renin. The transformation of AGT into ANG I is animal species specific, meaning that renin from one species better processes AGT from the same species than those from other species (10, 11, 99, 100). Renin is synthesized as an inactive proenzyme (prorenin) that becomes enzymatically active either through catalytic cutting off the NH2-terminal propeptide by a convertase or by a conformational change after its binding to the prorenin/renin receptor (PRR). Besides this enzymatic role, PRR may trigger intracellular pathways such as the MAP kinase p42/p44 and the phosphatidylinositol 3-kinase (PI3K)/p85 pathways (131).

ANG I gives rise to several angiotensins (Fig. 1A). ANG II is produced mainly from ANG I through the ANG-converting enzyme (ACE) and also by various chymases. ANG 1–7 may be synthetized from ANG I through neutral endopeptidase 24.11, called neprilysin, prolyl-endopeptidase, or polycarboxypeptidase. In addition, ANG 1–7 may be synthetized from ANG 1–9 through ACE or from ANG II through ACE type 2.

Fig. 1. A: enzymatic cascade of renin-angiotensin-aldosterone system (RAAS). The synthesis of angiotensins (ANG) results from the breakdown of angiotensinogen (AGT) by renin and is regulated by angiotensin-converting enzymes (ACE, ACE2) and by neprilysin (NEP). These enzymes are anchored on the endothelial cells of most blood vessels. ACE releases 2 amino acids at the COOH-terminal end of ANG I and ANG 1–9, whereas ACE2 releases 1 amino acid at the COOH-terminal end of ANG I, ANG 1–9, or ANG II. ANG II originates mainly from ANG I through ACE, whereas ANG 1–7 is essentially synthesized from ANG II by ACE2. Arrows indicate the cleavage site of the enzymes. B: RAAS pathways. The rate-limiting step of the system is the breakdown of AGT into ANG I by the enzymatic activity of renin. Aliskiren is a direct renin inhibitor that impairs the enzymatic action of renin but does not block renin’s association with the prorenin/renin receptor (PRR). ANG I is an inactive peptide that may produce ANG II and/or ANG 1–7. The synthesis of ANG II is inhibited by ACEI. ANG II acts on 2 receptors, ANG II receptor type 1 (AT1R) and ANG II receptor type 2 (AT2R). ANG 1–7 acts on its Mas receptor (MasR) and on AT2R. Angiotensin receptor blockers (ARB) are specific for AT1R. AT2R signaling is modulated by AT2R-interacting protein (ATIPs), which bind to the COOH-terminal tail of the receptor. AT1R and Mas receptor are G protein coupled. In contrast, mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) are cytosolic receptors that migrate into the nucleus and bind to DNA-responsive elements in the presence of the hormones. In humans, these receptors are activated by both aldosterone and cortisol. In white adipose tissue, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) increases cortisol production or corticosterone in rodents, thereby enhancing MR stimulation by glucocorticoids. Conversely, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) increases cortisone or dehydrocorticosterone in rodents, which cannot bind to MR, and thereby favors aldosterone binding to the MR. Eplerenone and spironolactone are MR antagonists. Sharp arrows indicate activation; blunted arrows indicate inhibition. Receptors are inside boxes.
(ACE2). The latter is the main enzyme for the synthesis of ANG 1–7. ACE is a dicarboxypeptidase that deletes two amino acids at the COOH-terminal end of ANG I, and ACE2 is a monocarboxypeptidase that removes one amino acid at the COOH-terminal part of ANG I and ANG II. ACE and ACE2 are glycophosphatidylinositol-anchored proteins that are present on the endothelial cells of most blood vessels. These enzymes may be released in the blood circulation after cleavage by proteins from the disintegrin and metalloproteinase family.

Although ANG I itself is not an active hormone, its derived molecules are. Indeed, ANG 1–7 acts on its Mas receptor (153) and on AT2R (183). In contrast, ANG II acts on two receptors (Fig. 1B). The AT1R mediates the main effects of ANG II and stimulates aldosterone secretion from the zona glomerulosa of the adrenal glands. The effects of AT2R are less clear. In pathological states, AT2R expression increases with tissue remodeling and inflammation (103). By heterodimerization with AT1R, it may interrupt AT1R signaling (3). In addition, the effects of AT2R vary with the cellular context and may be independent from ANG II (124). Indeed, AT2R is regulated by specific cytosolic partners called AT2R-interacting proteins (ATIPs) and/or by oligomerization of its receptor (149). For example, AT2R occupied by ATIP1 inhibits signaling of several tyrosine kinase receptors (132, 149). Remarkably, AT2Rs are usually expressed to a lower extent than AT1R, except in some tissues (endocrine and exocrine pancreas, brain stem, and testis) (160), whereas ATIP1s are expressed ubiquitously (132). AT1R, AT2R, and Mas receptor are G protein-coupled receptors. In general, AT1Rs are coupled to Gs protein, which is responsible for mobilization of intracellular calcium stores. However, AT1Rs may also be linked to other G proteins, and AT2Rs do not always couple to heterotrimeric G proteins. Aldosterone stimulates both mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). MR and GR are cytosolic receptors that migrate into the nucleus and bind to DNA-responsive elements in the presence of aldosterone or cortisol. MR may be stimulated by glucocorticoids, namely cortisol in humans or corticosterone in rodents. Circulating levels of glucocorticoids are 1,000-fold higher compared with aldosterone ones. Glucocorticoids are transformed by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and become inactive on MR (139). Conversely, they are reactivated by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). This latter enzyme is present in WAT, where it locally transforms cortisone into cortisol in humans or dehydrocorticosterone into corticosterone in rodents (120), thereby enhancing MR stimulation by glucocorticoids (Fig. 1B).

RAAS can be blocked pharmacologically at several levels (Fig. 1B). Aliskiren is a direct renin inhibitor that stops AGT breakdown but does not prevent the stimulation of PRR by renin. ACE inhibitors (ACEI) repress ACE and thereby most of the conversion of ANG I into ANG II and of ANG 1–9 into ANG 1–7. ANG receptor blockers (ARB) target the AT1R. Eplerenone, spironolactone, and canrenoate are MR antagonists. Importantly, all of these drugs, except aliskiren, increase renin release by interrupting a negative feedback loop of ANG II and aldosterone on renin production. Consequently, ACEI, ARB, and MR antagonists stimulate renin synthesis and AGT breakdown (123).

**RAAS Modulates Adipogenesis, Lipogenesis, and WAT Content of the Body**

A functional RAAS is necessary for normal adipogenesis and lipogenesis. Complete inhibition of RAAS through renin (172) or AGT (119) gene disruptions results in a lean phenotype with low body fat mass. The lack of molecular components of RAAS is responsible for this phenotype because it is reversible upon ANG II administration (172). Furthermore, alisikiren, which inhibits the production of all angiotensins, reduces body weight at the expense of fat mass in adult mice (81, 170). The PRR is probably involved in adipogenesis. Indeed, PRR activates the MAP kinase p42/p44 pathway (130) in the stromal cells of WAT (4), and MAP kinase p42/p44 is required for adipogenesis (14). However, the precise role of the PRR in WAT remains to be unraveled.

Adipogenesis and lipogenesis are regulated through complex mechanisms, including intrinsic modulation of RAAS receptors stimulated in an autocrine fashion (30, 116). This has been illustrated in 3T3-L1 fibroblasts, in which molecular components of RAAS participate in the differentiating process of fibroblasts to adipocytes (46, 80, 174). AT2R increases adipogenesis and lipogenesis by augmenting the expression of peroxisome proliferator-activated receptor gamma (PPARγ), a key transcription factor for adipogenesis, and fatty acid synthesis (FAS) production and activity (88, 163). In addition, MR upregulate PPARγ expression in differentiating 3T3-L1 adipocytes (19). The trophic role of AT2R in adipocytes is also illustrated by the phenotype of AT2R−/− mice. Indeed, these mice have small adipocytes even on a high-fat diet (195) despite high circulating levels of angiotensins (108). AT2R stimulation increases WAT mass in high-fat/high-fructose-fed rats (163) and augments adipose cell number in KKai mice (136). Mas receptor stimulates adipogenesis via the PI3K pathway (175). Its specific agonist, ANG I–7, is the main product found in supernatants of 3T3-L1 adipocytes exposed to ANG I (187). ANG II promotes the local synthesis of prosta-cyclin in adipocytes, which is a potent adipogenic factor (150). RAAS is also involved in a negative paracrine control of adipogenesis and lipogenesis. Indeed, mature adipocytes produce ANG II and block the differentiation of preadipocytes through AT1R (48, 83). ANG II may be processed into ANG 1–7 by local ACE2, and in turn ANG 1–7 stimulates lipolysis through its Mas receptor (135).

At least three lines of evidence support the idea that RAAS modulates energy balance and changes WAT content of the body. First, renin overexpression increases food intake. This is illustrated in transgenic (Tg) (mRen-2)27 rats with two murin renin genes (79) and Tg(hRen) rats expressing the human gene encoding renin (60). Second, ACEI and ARB reduce body WAT in rodents (43, 49, 128, 189). The decrease in body fat occurs by lowering food intake (31, 43) and possibly by increasing the metabolic rate. Energy expenditure was not measured in ACEI- or ARB-treated animals, but the decreased visceral fat mass observed in ACE−/− mice, mimicking ACEI, was found together with a high metabolic rate without change in alimentary intake (84). Weight modification following ACEI or ARB has never been monitored in humans, to the best of our knowledge. However, telmisartan decreases the area of intra-abdominal WAT measured by computer tomogram scanning at the level of the umbilicus (161), which is considered an
accurate estimate of the intra-abdominal fat volume in humans (61). Third, a pharmacological dose of ANG II induces weight loss at the expense of WAT. Indeed, ANG II given to rats reduces food intake (16, 20, 133) and/or increases energy expenditure (20, 32). Similarly, constitutive activation of RAAS in genetically modified mice with high ANG II levels in blood is responsible for a small fat mass and for resistance against diet-induced obesity (40).

Interestingly, several studies have established that energy balance is modulated by brain RAAS (142, 143), which is involved in the regulation of body WAT through the control of metabolic rate and food consumption (32). Regarding food intake, intracerebroventricular (icv) administration of ANG II increases the mRNA of corticotropin-releasing hormone in the paraventricular nucleus, leading to decreased food consumption in normal rats (142, 143). In mice, icv administration of ANG II suppresses hypothalamic neuropeptide Y and orexin production, resulting in lower food intake (194). In addition, brain AT1Rs increase energy expenditure and metabolic rate. Indeed, icv administration of ANG II to normal rats augments the expression of uncoupling protein 1 in brown adipose tissue (BAT) (143) and increases in BAT and WAT the number of β-adrenergic receptors (32), which are key players in lipolysis (98). Of note is that both leptin and RAAS are controlling the metabolic rate. In fact, leptin increases the sympathetic tone on BAT through brain AT1R, as demonstrated by icv administration of losartan (76). Constitutive activation of the RAAS in brain is obtained in double-Tg mice expressing human renin controlled by the neuron-specific synaptin promoter and human AGT controlled by its own promoter (63). These double-Tg mice have an increased sympathetic tone on BAT, resulting in leanness and decreased body WAT content (63). Remarkably, these double-Tg mice have decreased circulating ANG II levels, and parenteral administration of ANG II restores a normal metabolic rate (63). This suggests that brain and peripheral ANG II are balanced, with peripheral ANG II controlling the sympathetic stimulation on BAT (32, 64). Low brain penetrance of ACEI, ARB, and infused ANG II could also change the balance between brain and peripheral ANG II (64). This phenomenon might explain the paradoxical observation that weight loss results either from the blockade of the ACE-ANG II-AT1R-aldosterone axis by ACEI and ARB or alternatively from the stimulation of the same axis with ANG II administration. However, this remains to be teased out.

**Glucose Homeostasis, WAT, and the Metabolic Syndrome**

Schematically speaking, glucose homeostasis is governed by the control of insulin on fuel disposal in insulin-sensitive tissues and by hepatic glucose production (90). The integrity of pancreatic islets is critical for insulin production and release, whereas insulin clearance depends on insulin-degrading enzymes (115). The insulin receptor (IR) is a tyrosine protein kinase that undergoes rapid autophosphorylation when stimulated and phosphorylates thereafter its intracellular substrates IRS-1 and -2. Following tyrosine phosphorylation, IRS1 and -2 act as docking proteins for PI3K and several other molecules. PI3K activation via IRS1 and -2 appears to be the main cascade required for most of the metabolic actions of insulin. Put in a very simplified fashion, insulin actions include glucose uptake through glucose transporter 4 (GLUT4) translocation in skeletal muscle and adipose tissue, increased hepatic glycogen storage, decreased hepatic glucose production, enhanced lipogenesis, and decreased lipolysis in the WAT.

Both insulin secretion and action are modulated by complex mechanisms. For example, in the metabolic syndrome, increased oxidative stress blocks insulin secretion and GLUT4 translocation. Reactive oxygen species (ROS) stimulate c-Jun NH2-terminal kinases (JNK) and IkB kinase β (IKKβ), which induce the production of inflammatory cytokines (157). In turn, inflammatory cytokines are able to hamper insulin action by inducing IRS-1 phosphorylation on serine residues, perturbing its docking function (67).

WAT is a key tissue in the pathophysiology of the metabolic syndrome because it increases oxidative stress and produces adipocytokines, which contribute to insulin resistance. The blood levels of lipid peroxidation products, used as markers of oxidative stress, are increased in obese and insulin-resistant KKay mice, in the db/db mice, and following diet-induced obesity in mice (50). Of note is that in the obese KKay mice, augmented oxidative stress results from both high ROS production and decreased ROS scavenging from the WAT (50).

WAT’s secretory profile appears to be related to morphological changes, including adipocyte hypertrophy and recruitment of immune cells in WAT (188). In the metabolic syndrome, macrophages are attracted into the WAT. The migration is driven by a high level of proinflammatory T helper lymphocytes (Th1) together with fewer regulatory T lymphocytes (109, 110). In addition, Th1 secretory profile favors the switch from alternatively activated M2 macrophages into inflammatory M1 phenotype. The interaction between adipocytes and M1 macrophages plays a key role in the metabolic syndrome. Hypertrophic adipocytes release more fatty acids, which in turn stimulate the production of proinflammatory cytokines, including tumor necrosis factor-α (TNFα) and interleukin 6 (IL-6), in macrophages through Toll-like receptors 2 and 4 (157, 171). Furthermore, adipocytes produce monocyte chemoattractant protein-1 (MCP-1), which triggers macrophage infiltration of the WAT (91). Functionally, the accumulation of M1 inflammatory macrophages is associated with a molecular switch in the production of adipocytokines, with increased production of leptin (27, 117), IL-6 (45, 188), and TNFα (177) but a decreased synthesis of adiponectin (158). Globally, adiponectin improves insulin sensitivity (191), whereas IL-6 and TNFα promote insulin resistance. Leptin may increase peripheral insulin sensitivity through its brain receptors (126). In Kletsyks rats, which lack leptin receptors, restoration of leptin receptor expression in the arcuate nucleus improves insulin sensitivity mainly by decreasing hepatic glucose production (53). However, leptin levels are augmented in obesity, which corresponds to a state of leptin resistance. Therefore, the precise role of leptin in glucose homeostasis remains to be determined (29).
content of skeletal muscle and liver is linked to muscle insulin resistance (93) and nonalcoholic fatty liver disease (39, 47), respectively.

It is generally believed that adipogenesis occurs along with the growth process in children and that the adipose cell number is stabilized during childhood (96, 168). In adulthood, adipogenesis would account only for WAT renewal (192). Consequently, increased fat mass in human adults could reflect only adipocyte hypertrophy, which is associated with WAT inflammation. In contrast, in adult rodents adipocyte number may increase following a high caloric intake (87, 95). The augmented adipogenesis may be viewed as a protective mechanism against insulin resistance. Indeed, production of new adipocytes following troglitazone administration in obese Zucker rats (137) or following AT2R stimulation in high-fat/high-fructose-fed rats (163) or KKay mice (136) decreases the levels of inflammatory markers and improves insulin sensitivity.

Links Between RAAS, WAT, and Insulin Resistance

Remarkably, AGT, renin, ACE, and aldosterone blood levels are upregulated in obesity, and this is reversible after significant weight loss (37). In humans, the AGT blood level is positively correlated to the body mass index (178) and the aldosterone blood level to waist-over-hip ratio (58). Aldosterone is not synthesized in WAT because it lacks aldosterone synthase (140). Its production is driven by AT1R or by oxidized products of linoleic acid released from the WAT, which directly stimulates aldosterone production in the adrenal gland (35, 57). Increased expression of RAAS components intrinsic to the WAT has been found in obesity. Actually, AGT mRNA is augmented in WAT of obese mice secondary to high-fat diet (147), and both AGT mRNA and protein are increased in WAT of obese Zucker rats (71). In overweight humans, AGT and AT1R mRNAs are augmented particularly in visceral adipose tissue (54). In obese humans, 11β-HSD1 production is high in WAT compared with lean subjects (36), increasing cortisol production and allowing cortisol to activate MR locally. The modulation of RAAS intrinsic to WAT in obesity is in favor of its pathophysiological role in the metabolic syndrome. Indeed, in mice, genetically induced AGT overproduction from the WAT results in visceral obesity (118, 119). In addition, Tg mice with overexpression of 11β-HSD1 in WAT have hypertrophic visceral adipocytes; they are insulin resistant and hyperglycemic when submitted to an intraperitoneal glucose load (120).

Many lines of evidence support the fact that RAAS modulates macrophage seeding of adipose tissue and adipose tissue macrophage polarization, which are both potent triggers of insulin resistance. In an autocrine fashion, ANG II production intrinsic to the WAT stimulates MCP-1 release from adipose cells (102), which in turn contributes to the recruitment of macrophages into the WAT (Fig. 2A) (167). ANG II generated by adipocytes stimulates macrophages in a paracrine fashion and induces the production of MCP-1 and -2, thereby enhancing macrophage recruitment into the WAT (68, 176). Eplerenone given to db/db and ob/ob mice reduces the macrophage seeding of adipose tissue, as established by the lower levels of markers of inflammatory M1 macrophages found in WAT of treated mice compared with nontreated ones (77). In addition, the macrophage infiltration of adipose tissue decreases in chimeric KKay mice transplanted with bone marrow from mice overexpressing ATIP1 (86). Furthermore, RAAS modulates the ratio of M1 over M2 macrophages in WAT. Indeed, a macrophage M2 polarization pattern in WAT is achieved following a high-fat diet in AT1R subtype A-knockout mice (114), in ARB-treated mice (49), and following a high-cholesterol diet in mice with genetic overexpression of ATIP1 (86).

Links Between RAAS and Oxidative Stress in Key Tissues for Glucose Homeostasis

ROS in nonphagocytic cells are second messengers in many physiological processes controlled by RAAS (62). ROS production is driven mainly by nonphagocytic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which favors the reduction of oxygen into superoxide anions. Its precise structure and functions remain to be determined. However, it is accepted that this multiprotein complex is activated mainly by the assembly of the cytosolic p47phox protein subunit with the membrane-bound flavoprotein complex (33, 186). Of note is that apocynin represses p47phox binding to the membrane proteins and hence, impairs NADPH oxidase activity. Excess stimulation of NADPH oxidase or lack of antioxidative enzymes results in oxidative stress.

Oxidative stress is induced by the RAAS deleterious axis through NADPH oxidase in several cell types (62), including adipocytes (97), skeletal myocytes (50), hepatic stellate cells (33), and pancreatic β-cells. In WAT of obese and insulin-resistant KKay mice, ARB and apocynin decrease mRNA levels of components of NADPH oxidase and thereby decrease blood levels of peroxidized lipids, which are markers of oxidative stress (97). Consequently, ARB given to KKay mice raise the plasma levels of adiponectin, an insulin-sensitizing hormone (97). ANG II produced by adipocytes augments peroxide production from macrophages (193). In primary cultures of rat myocytes and in L6 myotubes, ANG II increases superoxide production by enhancing the translocation of cytosolic p47phox to the cell membrane (186). ARB or apocynin reverses this process (186). In the skeletal muscles of Tg (mREN-2)27 rats, p47phox protein augments together with local markers of oxidative stress. This muscular phenotype is reversible following aliskiren (99) or spironolactone administration (100), improving insulin-stimulated glucose uptake in isolated muscles from these animals (99, 100). In the liver, AT1Rs increase the activity of nonphagocytic NADPH oxidase in cultured hepatic stellate cells and promote the production of extracellular matrix components (8). Hepatic stellate cells are key for the development of liver fibrosis in the metabolic syndrome (47). Regarding pancreatic islets, ANG II augments locally the activity of NADPH oxidase (70). ANG II and aldosterone raise oxidative stress in pancreatic islets, induce islet fibrosis, and decrease insulin secretion (26, 113). In contrast, AT2R and Mas receptor increase insulin production (9, 160), and AT2Rs lower oxidative stress in pancreatic islets (159). Taken together, the increased oxidative stress induced by RAAS in key tissues for glucose homeostasis explains, at least in part, the paradoxical observation that ANG II-treated rodents are insulin resistant despite decreased adiposity. Indeed, in chronic ANG II-infused rats, euglycemic and hyperinsulinemic clamps show that glucose utilization rate is im---
Genetic Studies Linking RAAS and the Metabolic Syndrome in Humans

Genetic studies have suggested a possible link between RAAS and the metabolic syndrome in humans. Indeed, single nucleotide polymorphism analysis among 352 persons with the metabolic syndrome points to genetic loci involved in the production of RAAS components (125). ACE gene insertion/deletion (I/D) polymorphism is responsible for half of the variability of plasma ACE levels (85). However, the genotype linked to the metabolic syndrome is a matter of debate. Indeed, the deletion/deletion genotype is associated with a lower glucose tolerance in two independent populations of healthy adults, as assessed by an oral glucose tolerance test (12). In contrast, a meta-analysis showed that the I/D genotype would be linked to the risk of developing diabetes (197). In two German patient populations, aldosterone blood level within the normal range was higher in persons with traits of metabolic syndrome compared with healthy adults (72).

Fig. 2: A: RAAS deleterious axis regarding glucose homeostasis. The ANG II-ACE-AT1R-aldosterone axis induces insulin resistance and increases glycemia. Left: in adipocytes, AT1Rs inhibit the phosphatidylinositol 3-kinase (PI3K) cascade directly (arrow 1) and indirectly through increased oxidative stress (arrows 2–4). This latter effect involves c-Jun N-terminal kinase (JNK) and IkB kinase-β (IKKβ), which are activated by reactive oxygen species (ROS). Aldosterone and glucocorticoids inhibit the PI3K pathway through GR. AT1Rs promote the synthesis of interleukin-6 (IL-6) and monocyte chemoattractant protein 1 (MCP-1), leading to an insulin-resistant secretary profile and favoring the recruitment of macrophages in adipose tissue. MR promote the recruitment of macrophages, and AT1Rs change the polarity of alternatively activated macrophages (M2) into inflammatory ones (M1). M1 macrophages produce inflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNFα). ROS reinforce the production of these cytokines from adipocytes through JNK and IKKβ. AT1Rs inhibit adipogenesis and lipogenesis by decreasing the expression of fatty acid synthase (FAS) and peroxisome proliferator-activated receptor-γ (PPARγ). Left middle: in skeletal myocytes, AT1Rs inhibit the PI3K cascade directly (arrow 1) and indirectly through increased oxidative stress (arrows 2–4). This results in inhibition of glucose transporter 4 (GLUT4) translocation to the cell membrane and therefore lowers insulin-stimulated glucose uptake. Right middle: in hepatocytes, AT1Rs and MR stimulate gluconeogenesis through increased expression and production of phosphoenolpyruvate carboxykinase (PEPCK). This results in increased hepatic glucose production. Right: in β-cells, AT1Rs augment oxidative stress, promote apoptosis, and lower glucose sensing by suppressing GLUT2. In addition, aldosterone increases ROS production. The global effect of this RAAS axis is a reduced capacity for the production of insulin. B: RAAS beneficial axis regarding glucose homeostasis. RAAS beneficial axis improves insulin sensitivity and decreases glycemia. ANG 1-7-ACE2-Mas receptor pathway: in adipocytes (left), MasR inhibit the production of ROS and favor insulin actions through the PI3K cascade. MasR increase the production of adiponectin, an insulin-sensitizing hormone. In skeletal myocytes (left middle), MasR increase insulin-mediated glucose uptake through the translocation of glucose transporter 4 (GLUT4) to the cell membrane. In hepatocytes (right middle), insulin and MasR promote glycogen synthesis through stimulation of glycogen synthase. Insulin and MasR block the production of PEPCK, reducing gluconeogenesis. This reduces hepatic glucose production. Finally, MasR reduce the expression of the components of NADPH oxidase. In β-cells (right), MasR lower ROS production and protect the cell from apoptosis. ANG II-AT2R pathway: in adipocytes, the AT2Rs augment adipogenesis and lipogenesis by increasing the activity of FAS and the expression of PPARγ. ATIPs bound to AT2Rs reduce the seeding of macrophage into adipose tissue and augment the formation of alternatively activated M2 macrophages. In β-cells, AT2Rs lower oxidative stress and thereby augment insulin production capacity. ANG 1–7 may act through AT2Rs. In A and B, sharp arrows indicate activation, and blunted arrows indicate inhibition.
ACEI and ARB Improve Glucose Homeostasis in the Metabolic Syndrome

ACEI or ARB increase plasma levels of adiponectin (43). In humans, plasma adiponectin levels were found to be increased in 13 obese and glucose-intolerant patients treated for 1 mo with ARB (145) and in patients with metabolic syndrome treated for 6 mo (94). Increased adiponectin could be one of the factors contributing to improved insulin sensitivity after ACEI or ARB treatment. Indeed, in rodents, ARB lowered fasting glycemia, insulinemia, and plasma triglyceride levels (43, 128). ACEI increase glucose tolerance, as illustrated by the lower glycemic excursion after intraperitoneal glucose administration in mice (189). At the beginning of the clinical use of ACEI, cases of hypoglycemia have been reported with high doses of captopril and enalapril (122). In obese and glucose-intolerant patients (145), as well as in patients with central body fat accumulation (25), ARB improve insulin sensitivity. In contrast, in obese patients, losartan given for 3 mo does not modify the glucose incorporation rate assessed by euglycemic hyperinsulinemic clamp (107).

ACEI and ARB are used mainly in patients with hypertension and ischemic and/or hypertensive cardiopathy. Three clinical trials comparing ACEI with placebo showed a lower diabetes incidence with ACEI in large cohorts of patients with hypertensive and ischemic cardiopathy (1, 2, 15). It was further demonstrated that ARB increased patient survival and lowered diabetes incidence in large randomized controlled trials, including patients with hypertension or chronic heart failure (89, 105, 141).

In addition, two trials were designed specifically to test ACEI or ARB vs. placebo regarding diabetes incidence in humans. A lower diabetes incidence was observed with candesartan compared with placebo in more than 9,000 glucose-intolerant patients with ischemic cardiopathy (65), whereas ramipril did not change diabetes incidence but significantly lowered fasting glycemia after 3 yr in 5,000 overweight patients with glucose intolerance (13). Taken as a whole, a 20% reduction of the cumulative risk of new-onset diabetes has been documented with ACEI or ARB (5).

Aldosterone Blockade Improves Glucose Homeostasis

MR blockade with eplerenone increases adiponectin plasma levels in ob/ob and db/db mice (66, 77). In isolated visceral WAT, it decreases the expression of MCP-1, TNFα, and IL-6 (66, 77). Finally, it diminishes oxidative stress in isolated WAT (77). Furthermore, in pancreatic islets, aldosterone increases oxidative stress and lowers insulin secretion (113). Together, these mechanisms explain that MR blockade improves glucose tolerance and insulin sensitivity in ob/ob and db/db mice (77). They provide a molecular basis for the low-fasting glycemia observed in db/db mice treated with eplerenone (66). However, MR blockade for 6 wk in obese patients did not change insulin sensitivity measured by the homeostatic model assessment (HOMA) index (52).

Furthermore, increased aldosterone levels appear to be linked to insulin resistance in humans. In chronic heart failure, a higher aldosterone level within the normal range is independently associated with insulin resistance, as determined by the HOMA index (44). In healthy adults, stimulated aldosterone production decreases insulin sensitivity (51). Remarkably, MR is not the only target of aldosterone in the metabolic syndrome. Actually, in patients with Conn adenoma, surgical ablation of the tumor improves insulin sensitivity, whereas MR antagonism with spironolactone does not (164). In line with this, aldosterone-induced oxidative stress in WAT of mice is partly hampered by MR antagonists (77) as well as by GR antagonists (182). Finally, the effect of aldosterone on pancreatic islets from mice is not mediated by either MR or GR, but it is related to oxidative stress (113).

Dual RAAS Axis in the Metabolic Syndrome

The ACE-ANG II-AT1R-Aldosterone axis impairs glucose homeostasis and hence, favors diabetes. This is illustrated by low insulin sensitivity in Tg(mREN-2)27 rats with high tissue levels of ANG II and elevated plasma aldosterone levels (10, 99, 100). In contrast, the ACE2-ANG 1–7-Mas receptor pathway is protective against glucose intolerance. This is illustrated by the following lines of evidence: 1) Mas receptor-deficient mice (154) and ACE2−/− mice (173) are insulin resistant, and chronic ANG 1–7 infusion corrects the phenotype (173); 2) chronic ANG 1–7 infusion alleviates insulin resistance in fructose-fed rats (56); 3) insulin resistance induced by transient inactivation of the gene encoding IR is lowered by ANG 1–7 administration (156); 4) glycemic control of db/db mice improves following adenoviral expression of human ACE2 in the pancreas (9). The second pathway of the RAAS beneficial axis, the angiopoietin II-AT2R one, decreases insulin resistance because it augments plasma adiponectin levels (136), enhances insulin production (160), and protects β-cells from oxidative stress (159). In summary, it plays a major role in glucose homeostasis.

The ACE-ANG II-AT1R-Aldosterone Axis

In WAT, the deleterious RAAS arm reduces adipogenesis and triglyceride storage capacity and decreases plasma adiopensin levels, WAT inflammation, and local induction of oxidative stress (Fig. 2A). Concerning adipogenesis, in differentiating 3T3-L1 adipocytes, ARB increase the expression of PPARγ (48). In primary cultures of human preadipocytes, ARB increase the expression of FAS and PPARγ (83). Therefore, AT1R impair the fat storage capacity by inhibiting adipogenesis. In Otsuka Long-Evans Tokushima Fatty (OLETF) rats and in diabetic KKAY mice, ARB increase plasma levels of adiponectin (97, 102). In 3T3-L1 adipocytes, ARB increase the production of adiponectin (73). As detailed before, the same results are obtained with MR blockade in the ob/ob and in the db/db mice (66, 77). ARB lower the expression of MCP-1 in visceral fat from OLETF rats (102), and MR blockade produces the same effect in the ob/ob and in the db/db mice (66, 77). Moreover, eplerenone reduces macrophage infiltration of WAT (77). Therefore, AT1R and MR contribute to macrophage invasion of the WAT. In mice with genetic obesity or diet-induced obesity, AT1Rs change the profile of alternatively activated M2 macrophages to inflammatory M1 ones in WAT.
ARB decrease the expression of TNF-α and IL-6 from human adipocytes in primary culture (165), and in addition, AT1Rs directly augment the production of oxidative stress in 3T3-L1 adipocytes through GR (182). Insulin-induced glucose uptake in 3T3-L1 adipocytes is impaired by AT1R (48, 102) or by GR stimulation (182). Therefore, oxidative stress provides a strong link between the deleterious RAAS axis and insulin resistance in adipocytes. Indeed, the antioxidant molecule N-acetyl cysteine prevents GR reduction of insulin-mediated glucose uptake in 3T3-L1 (182). In addition, the antioxidant drug tempol restores insulin-induced glucose uptake in isolated WAT from ANG II-treated rats (133). Oxidative stress may block the PI3K pathway. Indeed, in 3T3-L1, GR-induced oxidative stress favors IRS-1 phosphorylation on Ser307 through IKKβ and target of rapamycin complex 1 (182), thereby blocking GLUT4 translocation to the cell membrane. However, oxidative stress-induced insulin resistance appears to be independent from this pathway. Indeed, in ANG II-treated rats, impaired insulin sensitivity of the WAT is found despite increased tyrosine phosphorylation of IR and IRS-1 and -2 together with robust serine/threonine phosphorylation of Akt in WAT and other insulin target tissues (134).

Concerning muscle tissue (Fig. 2A), in isolated muscles of KKα diabetic mice, ARB decrease TNFα expression and superoxide production, thereby improving insulin-mediated glucose uptake (162). Spiranolactone and aliskiren decrease ROS production in skeletal muscles of insulin-resistant Tg(mREN-2)27 rats and improve insulin-induced glucose uptake in their isolated muscles (99, 100). In addition, ANG II increases ROS in L6 myotubes and decreases insulin-stimulated glucose uptake. ROS scavenging following NADPH oxidase inhibition restores insulin’s action in L6 myotubes (186). Inhibition of the PI3K pathway accounts for the impaired insulin-induced glucose uptake in skeletal muscle of KKα mice, of Tg(mREN-2)27 rats, and in L6 myotubes (99, 162, 166, 186). However, chronic ANG II administration augments oxidative stress and impairs insulin action in rat skeletal muscles independently from the PI3K pathway (133). Finally, PPARβ production increases in isolated skeletal muscle following ARB administration in mice fed a high-fat diet. This augments glucose uptake through the PI3K pathway (104). In hepatocytes (Fig. 2A) of streptozotocin-induced diabetic rats, AT1Rs stimulate phosphoenolpyruvate carboxykinase (PEPCK) gene expression and production, a key enzyme of gluconeogenesis (21, 22). Moreover, in normal rats, ANG II augments oxidative stress and thereby decreases glycolysis synthase activity, the master enzyme for glucose storage (133). The result of these molecular processes is increased glucose production by the liver, favoring hyperglycemia (74). AT1Rs increase oxidative stress in hepatic stellate cells through NADPH oxidase activation (8). This process is involved in liver fibrogenesis, which may exacerbate liver steatosis related to the metabolic syndrome (47, 111, 185). Finally, transgenic renin overexpression in the liver augments insulin clearance and reduces glucose tolerance of mice submitted to an acute glucose load (41).

In isolated pancreatic islets (Fig. 2A), stimulation of AT1Rs (101) or overexpression of AT1Rs secondary to hypovitaminosis D in mice (23) lowers insulin release, resulting in glucose intolerance. Conversely, blockade of AT1Rs in human subjects suffering from the metabolic syndrome improves insulin secretion (181) despite the fact that chronic hyperglycemia would upregulate AT1Rs in pancreatic islets (24). ARB lowers the expression of NADPH oxidase in db/db mice and restores insulin production in β-cells (129). The silencing of AT1Rs with small interfering RNA in isolated pancreatic islets from db/db mice results in increased GLUT2 and glucokinase protein levels (196). Extrapolated to the organismal level, AT1R blockade would enhance the glucose sensitivity of the β-cells. Furthermore, aldosterone lowers glucose-induced insulin secretion in isolated pancreatic islets of mice. The antioxidant drug tempol restores insulin secretion from the islets (113). This suggests the involvement of ROS in the increased insulin secretion observed in aldosterone synthase-deficient mice (Cyp11b2−/−) (113).

The ACE2-ANG 1–7-Mas Receptor Pathway

In adipose tissue (Fig. 2B), Mas receptor causes lipolysis, as indicated by increased hormone-sensitive lipase phosphorylation and glycerol release, resulting in a lower visceral fat mass in normal rats (135). Accordingly, rats with high endogenous ANG 1–7 levels have a low visceral fat mass despite high caloric intake (155). In primary cultured murine adipocytes, Mas receptor activation lowers oxidative stress, increases adiponectin production, and improves insulin-induced glucose uptake (106). Rats expressing an ANG 1–7-producing fusion protein submitted to a high-fat diet have more anti-inflammatory IL-1β protein and less TNFα mRNA in their visceral WAT. However, insulin sensitivity is not affected by these modifications (155). In contrast, fructose-fed rats display increased insulin signaling in adipose tissue following chronic ANG 1–7 infusion, and this results in improved insulin sensitivity according to the HOMA index (56). Moreover, in rats with transient inactivation of the gene encoding IR, ANG 1–7 administration increases insulin signaling in adipose tissue and improves glycemic control (156).

Concerning skeletal myocytes (Fig. 2B), ANG 1–7 increases insulin-induced glucose incorporation in isolated skeletal muscle of normal rats (144). In fructose-fed rats, chronic ANG 1–7 administration results in enhanced insulin signaling in skeletal muscle and ameliorates insulin sensitivity (56).

Concerning hepatocytes (Fig. 2B), ACE2 overexpression increases insulin-induced glycogen synthesis, which is blocked by the Mas receptor antagonist in the HepG2 cell line (18). In addition, ANG 1–7 decreases the mRNAs of PEPCK and glucose-6-phosphatase, thereby decreasing gluconeogenesis (18). Furthermore, ANG 1–7 lowers oxidative stress by inhibiting NADPH oxidase component expression (18). Extrapolated to the whole body level, the global effect of these molecular processes would be a diminished hepatic glucose production, which could contribute to lower glycemia.

In isolated pancreatic islets of mice (Fig. 2B), AT1R protein increases, whereas ACE2 protein decreases, following ANG II chronic administration. Furthermore, glucose-induced insulin secretion is low compared with islets from nontreated mice (26). Adenoviral-driven overexpression of recombinant human
ACE2 in the pancreatic islets restores insulin secretion and lowers AT1R protein, thereby improving glycemic control in vivo (26). This phenomenon has also been demonstrated in db/db mice (9).

The ANG II-AT2R Pathway

Regarding adipose tissue (Fig. 2B), AT2R stimulation increases the triglyceride storage capacity by lowering adipocyte size but increasing adipocyte number in rats fed a high-fat/high-fructose diet (163). In these rats, insulin sensitivity increases (163). This is reminiscent of the effects of troglitazone in obese Zucker rats (137). Furthermore, a similar situation is found to be independent from PPARγ in KKAY mice (136). These morphological changes are associated with a lower production of TNFα but with an increased production of adiponectin from WAT, and together these contribute to increased insulin sensitivity in obese Zucker rats (136). Furthermore, genetic ATIP1 adiponectin from WAT, which results in increased insulin-mediated glucose uptake in isolated WAT (86). In primary cultures of rat preadipocytes, AT2Rs stimulate adipogenesis by the induction of FAS and PPARγ (163). In addition, AT2Rs increase FAS activity in 3T3-L1 adipocytes (88).

Concerning skeletal myocytes (Fig. 2B), ANG II is a trophic factor (59), thereby augmenting the main reservoir for insulin-induced glucose uptake. In line with this, an improved glucose tolerance following intraperitoneal glucose load was found in mice with constitutive RAAS activation and high ANG II levels (40).

In the liver (Fig. 2B), AT2R stimulation reduces the triglyceride content in rats fed a high-fat/high-fructose diet, which protects against nonalcoholic fatty liver disease (163).

In the endocrine pancreas (Fig. 2B), AT2R stimulation increases the β-cell mass in KKAY mice, and this results in augmented glucose-induced insulin production following an intraperitoneal glucose load (136). AT2R stimulation increases insulin production in normal rats (160). Remarkably, AT2R stimulation prevents β-cell damage following streptozotocin administration in rats, as demonstrated by the lower glycemia, lower water intake, and reduced diuresis observed in treated animals compared with control ones (159).

Blockade of the Deleterious RAAS Arm Results in Activation of the Beneficial One

It is tempting to suggest that the blockade of the deleterious axis is salutary for glucose homeostasis because the beneficial one is activated simultaneously. At least three different arguments support this idea (1). The first argument is that administration of ACEI, ARB, or MR antagonists results in increased AGT breakdown and hence, in augmented ANG production, which may activate only the two pathways of the RAAS beneficial arm (2). The second argument is the modulation of two RAAS components of the ACE2-ANG 1–7-Mas receptor pathway following ACEI administration or diet-induced obesity in mice. Indeed, ACEI increase the expression of Mas receptors in WAT, hence favoring lipolysis (135). The increased Mas receptor expression in WAT could partly explain that ACEI or ARB reduce WAT mass when they are given to obese Zucker rats or to high-fat-fed mice (49, 128, 189).

Furthermore, ACE2 is upregulated in WAT of high-fat-fed mice (69). This may promote ANG 1–7 synthesis from ANG II in WAT, which would favor adipogenesis, thereby limiting the toxicity of ectopic fat storage (3). The third argument is that ARB do better than ACEI regarding the reduction of diabetes risk. Indeed, the probability of new onset diabetes is twice less frequent following ARB than ACEI therapy given to patients suffering from hypertensive or ischemic cardiopathy (5). This might be accounted for by the stimulation of both pathways of the RAAS beneficial arm following ARB treatment. Indeed, ARB augment ANG II synthesis, which may stimulate either AT2R or Mas receptor after transformation into ANG 1–7 by ACE2, whereas ACEI block the synthesis of ANG II and impair the stimulation of the ANG II-AT2R pathway.

Perspectives for Novel Therapeutic Approaches

The stimulation of the RAAS protective arm is an area offering promises for new therapeutic approaches. Indeed, several experimental studies have already been performed in cardiovascular diseases (92, 169). We summarize here the experimental data regarding the modulation of glucose homeostasis.

An orally active nonpeptidic agonist of AT2R called compound 21 (C21) has been developed (184). Remarkably, its high affinity and selectivity for AT2R allows for a robust stimulation despite the low expression of AT2R in most adult tissues (180). For instance, C21 administration in normal rats was found to enhance insulin secretion in response to a glucose load (160). In addition, in high-fat/high-fructose-fed rats (163) and in KKAY mice (136), C21 treatment augmented insulin sensitivity by promoting adipocyte differentiation. Moreover, C21 appeared to lower islet oxidative stress induced by streptozotocin administration in mice, and by doing so, C21 protected the β-cells (159). Interestingly, C21 has no blood pressure-lowering effect (169). To the best of our knowledge, no clinical study is currently ongoing with C21 regarding glucose homeostasis.

Concerning stimulation of Mas receptors, ANG 1–7 administration improves glycemic control in high-fructose-fed rats (56). A nonpeptide orally active Mas receptor agonist has been developed because long-term delivery of therapeutic levels of ANG 1–7, which is actively degraded, may prove clinically difficult (190). However, to the best of our knowledge, this formulation has not been tested for the purpose of improving glucose homeostasis. Alternatively, oral ANG 1–7 packaged in cyclodextrine has been used, and it has improved glycemic control of rats with transient inactivation of IR (156). The local increase in ANG 1–7 levels may also be achieved by modulation of ACE2 activity. Indeed, adenovirus-driven expression of human ACE2 in the pancreas of db/db mice was found to improve glycemic control (9). The development of therapeutic strategies stimulating AT2R and Mas receptors is a challenging issue for the prevention and treatment of insulin resistance and of β-cell failure, both leading to diabetes. Despite promising results, so far no molecule has been taken into a drug development program in humans.

Conclusions

The treatment of patients suffering from hypertensive or ischemic cardiopathy with ACEI and ARB has been an obvious success story. Indeed, these drugs are able to reduce cardio-
vascular death, end-organ damage, and diabetes incidence. The molecular basis of the beneficial effects regarding glucose homeostasis have for the most part been elucidated. ACEI and ARB act through modulation of autocrine and paracrine production of RAAS actors in insulin target tissues and in the endocrine pancreas. In brief, ACEI and ARB improve insulin sensitivity by decreasing oxidative stress, lowering the production of deleterious adipocytokines, and reducing body fat content. Many lines of evidence suggest that these events may result from a virtuous circle, wherein the blockade of the RAAS deleterious axis would be reinforced by the activation of the RAAS beneficial ones. Currently, several approaches to stimulate the RAAS protective axis are likely to be the scope of intense research for the development of new therapeutic strategies against obesity and its metabolic complications, such as diabetes. Modulation of ACE2-ANG 1–7-Mas receptor and ANG II-AT2R pathways offer new therapeutic areas for reducing toxicity of ectopic fat storage and insulin resistance and for protecting β-cells from oxidative stress. The balance between brain RAAS and peripheral RAAS for the control of energy homeostasis appears to be a promising mechanism for combating obesity. Finally, a better understanding of the PRR between brain RAAS and peripheral RAAS for the control of energy homeostasis may open new avenues for prevention and treatment of obesity.

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No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

G.A.F. conception and design of research; G.A.F. performed experiments; G.A.F. analyzed data; G.A.F. interpreted results of experiments; G.A.F. prepared figures; G.A.F. and E.V.O. drafted manuscript; G.A.F. and E.V.O. edited and revised manuscript; G.A.F., V.L.E., and E.V.O. approved final version of manuscript.

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