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Invited Review

ScopeMed

Angiotensin antagonist drugs as "source antioxidants" – Down-regulation of nicotinamide adenine dinucleotide phosphate oxidase activation mediates many of their protective benefits, independent of hypertension control

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ABSTRACT

Angiotensin II (ATII), acting via Type I ATII receptors (AT1R), promotes vasoconstriction of vascular smooth muscle; hence, angiotensin antagonist drugs, i.e., angiotensin receptors blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors, are employed in the management of hypertension. However, AT1R stimulation also activates nicotinamide adenine dinucleotide phosphate oxidase complexes in a range of tissues, via joint stimulation of protein kinase C and Rac. Angiotensin antagonist drugs therefore function as "source antioxidants" preventing oxidative stress at its source by blocking superoxide production. This phenomenon may explain why these drugs have been found to convey a range of health benefits that are at least partially independent of their impact on blood pressure. These benefits appear to include: A reduction in risk for Type 2 diabetes; an improvement in endothelial function; reduced risk for vascular disorders including atrial fibrillation, left ventricular hypertrophy and aortic aneurysms; reduced mortality in, and a possible preventive impact on, chronic obstructive pulmonary disease; slowed progression of kidney disease; slowed progression of diabetic neuropathy and retinopathy; decreased risk for non-alcoholic fatty liver disease; neuroprotective effects which may aid prevention of Parkinson's and Alzheimer's diseases; and an inhibitory impact on induction and spread of prostate cancer. There is reason to suspect that each of these benefits is largely attributable to the source antioxidant activity of ARB and ACE inhibitors. In light of the versatility of the protection afforded by these drugs, and the low risk for side effects with ARB, consideration should be given to the possibility of using ARB as a preventive measure in the general population (excluding pregnant women), in non-hypertensives and hypertensives alike - perhaps as a component of a "polypill." Moreover, the broadly favorable clinical experience with angiotensin antagonist drugs suggests that source antioxidants as a class may have far greater potential for preserving health than antioxidants which merely act as oxidant scavengers.

KEY WORDS: Angiotensin converting enzyme inhibitors, angiotensin, angiotensin receptor blockers, nicotinamide adenine dinucleotide phosphate oxidase, spirulina, telmisartan

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ACTIVATION OF NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE (NADPH) OXIDASE (NOX) BY TYPE 1 RECEPTORS FOR ANGIOTENSIN II (ATII)

The multiple pathogenic effects of excessive ATII activity are mediated primarily by its interaction with the angiotensin Type 1 receptor (AT1R), a seven-pass receptor coupled to various heterotrimeric G proteins. Stimulation of this receptor, in turn, promotes activation of Nox complexes via several independent pathways that interact in a complementary fashion; the mechanisms involved are somewhat tissue specific, and vary depending on the isoforms of Nox expressed in a given tissue [1-3]. Key downstream effectors of this activation are protein kinase C (PKC) and Rac1, which promote the plasma membrane assemblage of Nox1- and Nox2-dependent forms of Nox. In cells expressing Nox2, PKC phosphorylates p47phox, promoting its translocation to the plasma membrane, whereas

activated Rac1 serves as a bridge between this factor and Nox2. Analogously, in cells expressing Nox1, PKC promotes membrane translocation of Nox organizer 1 via phosphorylation and activated Rac1 binds to it and Nox1.

AT1R stimulation leads to activation of $G\alpha_q$, which in turn activates phospolipase C (PLC)-β. The resulting cleavage of membrane phospholipids generates diacylglycerol (DAG) and inositol-1,4,5-triphosphate. The latter stimulates release of calcium from the endoplasmic reticulum, such that cytosolic calcium levels rise, an effect which mediates a portion of ATII's vasoconstrictive impact on vascular smooth muscle. However, this rise in cytosolic calcium and DAG also can activate various forms of PKC, thereby promoting assemblage of Nox complexes. This activation of PKC is further prolonged by AT1R's activation of phospholipase D2 (PLD2), which generates phosphatidic acid by cleaving membrane phosphatidylcholine; subsequent cleavage of phosphatic acid yields DAG, helping to sustain activation of PKC. Activation of PLD2 by AT1R may be mediated by Gβγ and $G\alpha_{12/13}$ [3,4].

AT1R's activation of Rac1 is downstream from phosphatidylinositol-3-kinase (PI3K) activation; the latter generates phospholipids that bind and activate a Rac guanine nucleotide exchange factor that in turn induces binding of guanosine-triphosphate to Rac, activating it [5,6]. The mechanisms whereby AT1R stimulates PI3K activity are complex and still rather poorly defined, varying according to cell type. In vascular smooth muscle, activation of c-Src (proto-oncogene tyrosine-protein kinase) and subsequent transactivation of the epidermal growth factor receptor mediate this effect [7], whereas in some other cell types these agents are not required for AT1R's activation of PI3K [1].

In some tissues such as vascular smooth muscle, AT1R-mediated activation of phospholipase A2 (PLA2) contributes to the activation of Nox1 or Nox2. The mechanism of this effect is poorly understood but requires metabolism of the arachidonic acid released by PLA2 activity [8]. PLA2 and free arachidonic acid are also crucial to Nox activation in neutrophils [9]. The signaling pathways thought to be primarily responsible for AT1R-mediated activation of Nox1 and Nox2-dependent Noxs are outlined in Figure 1.

The other commonly expressed form of Nox, Nox4, is also activated by AT1R in various cell lines [10-13]. The basis of this effect remains unclear, although PLC and PKC activation play mediating roles; increased expression of Nox4 may be involved. ATR1 signaling can also up-regulate expression of various subunits of the Nox1- and Nox2- dependent forms of Nox; this is a slow-acting effect that contributes to the sustained activation of NADPH induced by ATII [2]. RhoA/Rho kinase activation mediates this induction in some tissues [14].

ANGIOTENSIN ANTAGONIST DRUGS AND BILIRUBIN ARE "SOURCE ANTIOXIDANTS"

Although AT1R's activation of Nox complexes is not essential to the vasoconstrictive and hypertensive impact of ATII (albeit it has an up-regulatory impact in this regard [2]), it is suspected to play a mediating role in many of the other adverse health effects associated with ATII over-activity [2]. Conversely, the versatile health protection afforded by treatment with drugs that oppose ATII activity, i.e., angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), may reflect, in large part, their antioxidant activity. These drugs might be characterized as "source antioxidants," in the sense that they go to the root of oxidative stress, blocking superoxide production at its source. Such antioxidants are inherently far more consequential than scavenging antioxidants, such as vitamins E or C, because they prevent the pro-inflammatory, pro-proliferative effects of hydrogen peroxide on signaling pathways, as well as certain direct effects of superoxide (such as nitric oxide [NO] quenching) that scavenging antioxidants cannot influence [15-18]. Hence, it is not surprising that, whereas ATII-antagonist drugs are emerging in clinical research and epidemiology as highly protective, independent of their impact on blood pressure, clinical trials with antioxidant vitamins have yielded paltry or even negative outcomes [19].

Recent studies show that free bilirubin functions intracellularly as a source antioxidant. When generation of reactive oxygen species (ROS) within cells promotes increased expression of heme oxygenase-1 (HO-1), the free bilirubin evolved by this enzyme can inhibit Nox complexes, which are often the source of the inciting ROS (the isoform specificity of bilirubin's impact in this regard still awaits clarification). Hence, HO-1 and bilirubin function in a feedback loop that protects cells from Nox-mediated oxidative stress. The fact that subjects with Gilbert's syndrome, a genetic variant characterized by a chronic elevation of plasma free bilirubin levels, have been found to have an age-adjusted total mortality rate roughly half as high as that of subjects without this syndrome, and that relatively elevated bilirubin levels are associated prospectively with lower risk for cardiovascular events, chronic obstructive pulmonary disease (COPD) and certain cancers, may be viewed as evidence that source antioxidants can be profoundly health protective [20-24]. The protection afforded by ATII antagonist drugs may be somewhat more limited, inasmuch

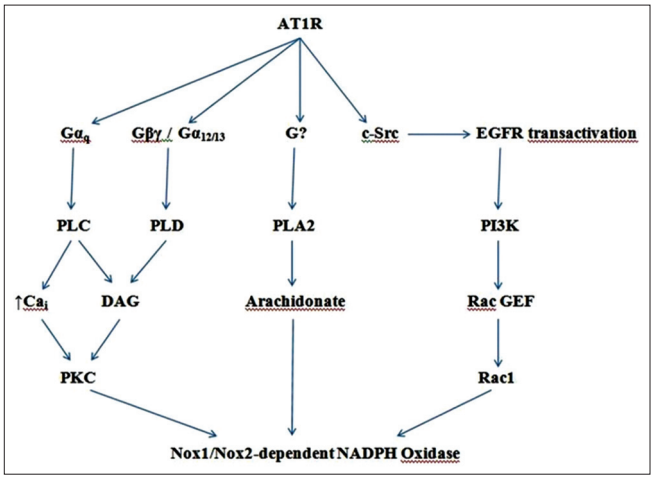

Figure 1: Signaling pathways mediating Type 1 angiotensin II receptor activation of nicotinamide adenine dinucleotide phosphate oxidase

as it will only extend to those tissues which express AT1R and other components of the renin-angiotensin system (RAS); nonetheless, a survey of current evidence indicates that suppression of AT1R activity can have a wide-ranging favorable impact on health.

With respect to many of the likely health benefits of ARB therapy in hypertensives, there is reason to suspect that down-regulation of Nox activity in tissues expressing AT1R may be a key mediator of these benefits.

Prevention of Non-Insulin-Dependent Diabetes Mellitus (NIDDM)

A survey of randomized controlled trials with ARB and/or ACE inhibitors concludes that hypertensives using these drugs, as opposed to other anti-hypertensive agents or placebo, are less prone to develop Type 2 diabetes [25]. This effect appears to reflect preservation of beta cell function as well as a modest improvement of insulin sensitivity [26-29]. On the other hand, telmisartan's favorable impact on insulin sensitivity may also reflect its clinical peroxisome proliferator-activated receptor-gamma (PPARγ) agonist activity [30-32]. Analogously, treatment with telmisartan prevents development of diabetes in spontaneously diabetic torii rats [31]. Activation of Nox in beta cells appears to be a key means by which glucolipotoxicity provokes a failure of glucose-stimulated insulin secretion and an up-regulation of apoptosis [33]. *In vitro*, telmisartan and candesartan have been shown to suppress the activation of Nox provoked by palmitate exposure [34,35], demonstrating that, even *in vitro*, generation of ATII coupled with AT1R activation has an up-regulatory impact on Nox activity in beta cells [36,37]. With respect to the favorable influence of angiotensin antagonists on insulin sensitivity, ATII is actually an adipokine which can act on AT1R expressed by adipocytes [38,39]; indeed, stimulation of AT1R in adipocytes appears to underlie the adverse effects on HIV protease inhibitor drugs on adipocyte function [40]. In genetically obese mice, activation of Nox in adipocytes has been shown to mediate the insulin resistance associated with adipocyte hypertrophy [41]. Epidemiologically, elevated plasma levels of free bilirubin (in patients with normal hepatic function) correlate with reduced subsequent risk for NIDDM [42-45]. And administration of the bilirubin precursor biliverdin to db/db diabetes-prone mice has been reported to slow their development of glucose intolerance, an effect associated with partial preservation of the proper differentiation state of beta cells [34].

Improvement of Vascular Endothelial Function

Treatment with angiotensin antagonist drugs tends to improve endothelium-dependent vasodilation and dampen endothelial inflammation [46,47]. This likely reflects the fact that endothelial cells express AT1R receptors capable of activating Nox [48-50]. ACE inhibitors also promote endothelial NO production by boosting bradykinin levels [51], an effect however which mediates their most common side effects, cough and angioedema [52,53]. The superoxide produced by Nox directly scavenges NO and also promotes the uncoupling of endothelial NO synthase (eNOS), converting it to a further source of superoxide. This oxidant-mediated uncoupling of eNOS reflects such mechanisms as oxidation of its cofactor tetrahydrobiopterin, down-regulation of dihydrofolate reductase expression, and glutathionylation of eNOS [54-58]. ATR1 can also compromise eNOS activity by activating RhoA/Rho kinase, which can decrease the stability of eNOS mRNA, and also boost expression of arginase 1 [59-61]; this activation may be downstream from Nox activation [62]. In addition, the superoxide produced by Nox can up-regulate nuclear factor (NF)-kappaB activation, stimulating endothelial inflammation [63-65]. Hence, endothelial Nox activity has been proposed as a key target for promotion of vascular health [19,66-69]. The lesser risk for cardiovascular events associated with elevated plasma bilirubin levels may reflect bilirubin's ability to inhibit Nox [22,23,70].

Prevention of Vascular Events

Studies clearly establish that ACE inhibitors reduce risk for myocardial infarction (MI) and stroke in at-risk subjects [71,72]. This likely reflects their favorable influence on both blood pressure and endothelial function. However, perplexingly, ARB as a class fail to prevent vascular events [73-75]. Indeed, in studies comparing ARB with placebo, ARB are not effective in this regard, despite their influence on blood pressure, and some studies even show a trend favoring placebo [74]. This conundrum is known as the "ARB - MI paradox" [76]. The likely explanation is that ARB therapy causes a reflex up-regulation of ATII production [77], and that ATII receptors other than AT1R exert a countervailing negative impact on risk for vascular events, perhaps by destabilizing plaque [73]. Indeed, stimulation of AT2R has been reported to increase matrix metalloproteinase production by monocytes and vascular smooth muscle cells [78,79]. AT2R also oppose angiogenesis, a process which is protective in the ischemic myocardium [80].

A fortunate exception in this regard is telmisartan, which was considered non-inferior to ramipril for prevention of vascular events in the massive ONTARGET multicenter randomized controlled trial [81]. The superiority of telmisartan over other ARB in this regard may reflect the ability of this drug to promote PPARγ activity, thereby ameliorating the impact of metabolic factors on vascular event risk. Moreover, agents which stimulate PPARγ tend to stabilize plaque by suppressing production of matrix metalloproteinases [82-86], an effect which would presumably counteract the adverse effect of AT2R in this regard.

Prevention of Atrial Fibrillation

A number of recent meta-analyses conclude that treatment with angiotensin antagonist drugs is effective in the primary prevention of atrial fibrillation, and also can reduce risk for recurrence of this disorder [87-92]; one dissenting review and meta-analysis doubts that ARBs are useful in secondary prevention, citing four recent trials which failed to observe an effect [93-96], and suggesting that publication bias skews the pertinent literature [97]. Growing

evidence, obtained from rodent as well as clinical biopsy studies, incriminates atrial oxidative stress, stemming at least in part from Nox, as a mediator of atrial fibrillation [98-104]. Oxidative activation of calcium/calmodulin-dependent protein kinase II may serve as a mechanistic link between oxidative stress and this disorder [105,106]. No studies correlating plasma bilirubin with risk for atrial fibrillation have been reported. Telmisartan's marked efficacy for prevention of atrial fibrillation, found to be superior to carvedilol in this regard [107], might be mediated in part by its PPARγ agonism [108]; thiazolidinediones are protective in rodent models of this disorder, and a prospective cohort study found that diabetics taking these drugs experienced less atrial fibrillation than diabetics receiving other medications [109-111].

Prevention of Left Ventricular Hypertrophy (LVH)

Although anti-hypertensive treatment per se is useful for the prevention and treatment of LVH, ARB and ACE inhibitors have emerged as more effective in this regard than beta-blockers or diuretics, assuming that equivalent reductions in blood pressure are achieved [112-116]. As in the case of atrial fibrillation, ventricular oxidative stress generated by Nox, notably the Nox2 and Nox4 forms, is believed to play a key mediating role in LVH [117-125]. Inducers of HO-1 are protective in rodent models of LVH [126,127].

Prevention of Aortic Aneurysms

ATII can promote formation of aortic aneurysms in rodents, and there is recent evidence that treatment of hypertensives with ARB or ACE inhibitors may reduce risk for aortic aneuryms more effectively than treatment with other anti-hypertensive drugs [128,129]. Rodent studies as well as clinical biopsy studies have implicated elevated Nox activity as a mediator of aneurysm formation [130-137].

Of related interest is the possibility that angiotensin antagonist drugs may decrease risk for mitral valve prolapse – like aortic aneurysm, a common feature of Marfan and Marfan-like syndrome. Myxomatous mitral valve disease appears to be driven by a fibrotic response to excessive transforming growth factor (TGF)-β activity within the mitral valve, whether in idiopathic mitral prolapse, or that associated with Marfan syndrome [138-141]. AT1R activation tends to up-regulate TGF-β signaling [142-144], likely in part because Nox activity is crucial to TGF-β-driven signaling pathways within fibroblasts that promote a phenotypic shift to myofibroblast behavior with matrix remodeling [145-149]. In mitral valve tissue cultured from patients with prolapse, exogenous TGF-β stimulated increased matrix production, and this response was inhibited by co-exposure to ARB [138]. TGF-β over activity is a fundamental mediator of Marfan syndrome and the benefit of ARB therapy in this syndrome is now being assessed in a multi-center controlled trial [143,149,150].

Prevention of COPD

Epidemiological analyses have observed reduced mortality in patients with COPD who use angiotensin antagonist drugs and/or statins [151-153]. There is reason to suspect that this may in part reflect a favorable impact on the inflammatory process that damages lung structure. A survey of smokers found that those expressing the high-expression DD genotype of ACE were twice as likely to experience COPD [154]. Subsequent studies have confirmed this association in Asian populations, albeit not always in European ones [155-157]. In mice exposed to cigarette smoke, TGF-β has been shown to play a mediating role in the destruction of lung architecture that occurs, and either a neutralizing antibody to this hormone, or treatment with losartan, has been shown to afford protection in this regard [158]. Analogously, in a mouse model for emphysema induced by tracheal instillation of elastase, concurrent treatment with irbesartan was associated with better lung compliance and longer running distance [159]. Angiotensin antagonist drugs are likewise protective in rodent models of pulmonary fibrosis [160].

There is considerable reason to suspect that Nox over-activation plays a mediating role in inflammatory lung damage [161-165], albeit one seemingly paradoxical mouse study reports that genetic knockout of Nox2 activity enhances susceptibility to cigarette smoke-induced lung damage in mice [166]. Also speaking to a role for Nox in the genesis of COPD is the fact that, prospectively, elevated serum levels of bilirubin correlate with reduced risk for both COPD and lung cancer [21]. Thus, although there is insufficient evidence at present to conclude that angiotensin antagonist therapy can reduce risk for COPD, there is good reason to suspect this, and such drugs do have a favorable clinical impact on patients with pre-existing COPD. And the protection afforded by statin therapy in COPD might also reflect an antioxidant effect (see below).

Slowing Progression of Kidney Disease

ARB and ACE inhibitors have emerged as more effective than other anti-hypertensive agents in slowing the progression of nephropathy, and these agents have also been found to be effective for slowing kidney disease progression in non-hypertensives [167-171]. Not surprisingly, oxidative stress stemming from Nox and mitochondria has been found to play a mediating role in rodent models of diabetic nephrophathy [172-176]. Oral administration of biliverdin can prevent nephrosclerosis in diabetic mice [177]. In rodent models of nephrophathy, the AT2R plays a protective role [178-181], and hence it is conceivable that up-regulated AT2R activity contributes to the renal protection afforded by ARB. Telmisartan was superior to losartan for improving renal function in hypertensive diabetics in the AMADEO trial, despite comparable reductions in blood pressure [182]; this may reflect telmisartan's PPARγ agonism, as this drug shows renal-protective effects in AT1R-knockout mice that are abrogated by an antagonist of PPARγ [183].

Slowing Progression of Diabetic Neuropathy and Retinopathy

Following an open pilot clinical study in which lisinopril treatment was found to improve motor and sensory nerve

conduction velocities as well as temperature and vibration perception thresholds in patients with diabetic neuropathy [184], a 1-year double-blind trial with the ACE inhibitor trandalopril in 41 normotensives with mild neuropathy observed significant improvements in peroneal nerve conduction velocity and sural nerve action potential amplitude in those receiving the drug [185]. A contemporaneous 1-year controlled study found that the ACE inhibitor quinapril had a beneficial impact on diabetic autonomic neuropathy [186]. In rodent models of diabetic neuropathy, ACE inhibitors as well as an ARB were reported to improve neural conduction velocity while reversing the diabetes-induced declines in epineural blood flow and endothelium-dependent vasodilation; one study concluded that net benefit in this regard was greater when therapy commenced soon after diabetes induction, and saw a greater response to an ACE inhibitor than an ARB [187-189]; the latter finding might reflect a favorable influence of bradykinin on the course of diabetic neuropathy [190]. A recent meta-analysis concludes that the DD genotype of the ACE gene, associated with increased ACE blood levels, associates with increased risk for neuropathy in diabetics [191]. Considerable evidence incriminates oxidative stress as a central mediator of diabetic neuropathy, and two studies have found that administration of the Nox inhibitor apocynin ameliorates this condition in diabetic rats, pointing to Nox as an important source of this oxidative stress [192-194]. A cross-sectional study evaluating nearly 3000 Type 2 diabetics found that autonomic neuropathy was more common in patients with relatively low serum bilirubin [195].

Angiotensin antagonist drugs may also have potential for slowing progression of diabetic retinopathy [196]. The RAS is expressed in the retina and ATII activity can provoke both increased capillary permeability and VEGF production, cardinal features of the pathology of diabetic retinopathy [197]. After two controlled pilot trials with captopril demonstrated a favorable effect of this agent on retinal capillary permeability in normotensive Type 1 diabetics [198,199], the EUCLID 2-year randomized trial of lisinopril therapy, likewise targeting normotensive Type 1 patients, found that risk for progression of retinopathy was reduced by about 50% in the treated subjects [200]; this result was however marred by the fact that HbA1c was significantly lower at baseline in the treated group. The subsequent controlled DIRECT studies examined the impact of candesartan on prevention or progression of retinopathy in both Type 1 and Type 2 diabetic patients. In Type 1 patients, candesartan was shown to reduce the incidence of retinopathy, but did not influence progression [201]. In Type 2 patients (all of whom had mild-to-moderate retinopathy at baseline), a non-significant reduction in risk for progression was seen with candesartan, but regression of retinopathy was significantly more common in the treated group, and retinopathy overall was less severe in those receiving candesartan [202]. A further controlled trial compared enalapril, losartan, and placebo in type 1 diabetics over 5 years of follow-up; those receiving the enalapril and losartan were 65 and 70% less likely to experience notable progression of retinopathy as contrasted to those on placebo [203]. Although elevated blood pressure is a risk factor for progression of retinopathy, these benefits were found to be independent of modification of blood pressure. A number of studies in diabetic rodents point to Nox activity as a mediator of retinopathy [204-207]. And several epidemiological studies have found that higher serum bilirubin levels are associated with lower risk for retinopathy in diabetics; most notably, diabetics with Gilbert's syndrome were only about one-third as likely to have retinopathy, after multivariate adjustments, than diabetics without this syndrome [208-211].

Prevention of Non-alcoholic Fatty Liver Disease (NAFLD)

A number of rodent studies conclude that angiotensin antagonist drugs can ameliorate the course of NAFLD, preventing not only hepatic fat deposition and steatohepatitis, but fibrosis and hepatocarcinoma as well [212-222]. A recent study evaluating 290 hypertensives with documented NAFLD observed that patients using angiotensin antagonists were about half as likely to have advanced fibrosis [223]. A pilot clinical trial found that treatment with telmisartan or olmesartan lowered serum alanine aminotransferase and improved insulin sensitivity in patients with NAFLD and chronic hepatitis C [224]. Controlled studies of these agents in patients at risk for NAFLD are warranted [225]. Nox activation in Kupffer and stellate cells appears to be a key mediator of hepatic fibrosis [226]. As noted, Nox activation in adipose tissue plays a role in inducing adipocyte insulin resistance, which results in excessive hepatic fat influx. Owing to its PPARγ agonist activity in adipocytes, telmisartan may be a particularly appropriate tool for managing NAFLD; PPARγ not only promotes adipocyte insulin sensitivity, but it also boosts production of adiponectin, an adipokine that acts directly on the liver to counteract fat deposition [227-232].

Prevention of Dementia and Parkinson's disease (PD)

Pro-inflammatory activated microglia, via generation of nitroxidative stress and pro-inflammatory cytokines, are suspected to play a mediating or exacerbating role in neurodegenerative disorders such as PD and Alzheimer's disease (AD). ATII can be generating within the brain, and via AT1R promotes microglial inflammation, including activation of microglial Nox [233,234]. On the other hand, ATII-mediated stimulation of AT2R exerts a neuroprotective anti-inflammatory impact on the brain, giving rise to the thesis that ARB may be more appropriate than ACE inhibitors for preservation of brain health [235-237]. There is a recent report that hypertensives with high cumulative use of ARB or ACE inhibitors are at decidedly lower risk for PD; centrally acting calcium channel blockers also were found to be protective in this study [238]. Angiotensin antagonism has often been found to be protective in rodent models of PD [239-243].

With respect to dementia risk, a prospective cohort analysis of the U.S. Veterans' Affairs data base (over 819,000 subjects) compared risk for incident dementia in subjects treated with ARB, lisinopril and other cardiovascular drugs. Those receiving ARB were 19% less likely than lisinopril users to develop dementia, and 24% less likely than users of other cardiovascular

drugs. Among subjects who had already been diagnosed with dementia, use of ARB, as opposed to lisinopril or other drugs, were notably less likely to be admitted to a nursing home, and also had a lower mortality rate [244]. In contrast, a smaller Taiwanese analysis (16,000 subjects) failed to observe a protective effect of ARB in regard to Alzheimer's risk [245]. A meta-analysis incorporating 19 randomized controlled trials and 11 prospective cohort studies enrolling hypertensives found that ARB use, when compared to use of beta-blockers, diuretics, or ACE inhibitors, was associated with better preservation of cognitive function and lower risk for dementia [246]. ARBs have been found to be protective in mouse models of AD; in those studies employing telmisartan, the PPARγ agonist effect of this drug was found to be partially responsible for the protection observed [247-250].

Prevention of Prostate Cancer

Although treatment with angiotensin antagonist drugs does not appear to decrease overall cancer risk, and some studies even suggest a small increase in risk [251-253], there is evidence that ATII, acting via AT1R expressed in the prostate and a high proportion of prostate cancers, plays a role in the genesis and aggressive spread of prostate cancer. ATII levels in seminal fluid are relatively high, reflecting a physiological role for this hormone in the fertilization process [254]. ATII acts on most prostate cancer cell lines to promote proliferation, angiogenesis and invasion, and boost expression of the androgen receptor [255-260]. ARB treatment slows the onset of prostate cancer in transgenic rat for adenocarcinoma of prostate (TRAP) rats genetically prone to this cancer, and slows the growth of prostate cancer xenografts in nude mice [257,258,261-263]. Men carrying the deletion (D) allele of the ACE gene, associated with increased expression of the ACE protein, have been found to be at increased risk for prostate cancer or advanced prostate cancer [264-266]. Conversely, a prospective cohort study found a trend for decreased mortality from prostate cancer in men using ARBs or ACE inhibitors, and pilot clinical studies and case reports indicate that ARB treatment may decrease prostate-specific antigen (PSA) levels or increase PSA doubling time in some men with recurrent prostate cancer [267-269]. These studies correlate nicely with multiple reports that Nox activity is elevated in many prostate cancers, and contributes to their proliferation and spread [270-280]. Moreover, administration of the Nox inhibitor apocynin has a cancer-preventive impact in TRAP rats [281].

In light of evidence that PPARγ agonists may have potential for prevention or control of prostate cancer, telmisartan may merit special consideration as an agent for controlling this malignancy [259,282,283]. ARB may in fact have potential for slowing the growth and spread, and boosting the chemosensitivity or radiosensitivity, of a broad array of cancers [284-286]. Indeed, a significant proportion of many types of cancer are reported to express AT1R, and stimulation of this receptor promotes activation or expression of mediators of aggressive spread and chemoresistance such as PI3K-Akt, NF-kappaB and VEGF. In xenografted nude mice, ARB have been reported to slow the growth of human cancers of the pancreas, bladder, stomach, lung, kidney, colon, ovary and uterine endometrium, as well as a glioma and an osteosarcoma [287-299]. ARB may be superior to ACE inhibitors for this purpose, as AT2R is expressed by some cancers and tends to exert an anti-proliferative effect [300-303]. Again, telmisartan is a particular interest, as its PPARγ agonism may give it a broader spectrum of anti-cancer activity [259,304-307]. Angiotensin antagonist drugs may also have potential for promoting improved chemo/radiosensitivity in desmoplastic tumors, characterized by a high content of fibroblasts, collagen and hyaluronan that compromise tumor blood flow by compressing vessel lumens, by exerting an anti-desmoplastic effect that boosts tumor perfusion [308].

PREVENTIVE HEALTH POTENTIAL OF SOURCE ANTIOXIDANTS

This brief survey indicates that, in addition to their utility for hypertension control, angiotensin antagonist drugs may have a favorable impact on the healthful function of many tissues which express AT1R, likely in large part owing to their source antioxidant activity. More specifically, such drugs, in addition to their utility as anti-hypertensive agents, appear to have potential for prevention of NIDDM, thrombotic vascular events, a range of vascular disorders including atrial fibrillation, LVH, and aortic aneurysms, nephropathy, common neurodenerative disorders (PD, AD) and prostate cancer.

Two implications can be drawn: First, consideration should be given to the possibility of administering moderate doses of angiotensin antagonist drugs, in particular ARBs, for which tolerance tends to be excellent (at least in hypertensives), as a preventive measure in normotensive subjects. The utility of such therapy for prevention of vascular events in non-hypertensives has been demonstrated [309]. Inclusion of moderate doses of an ARB, preferably telmisartan, owing to its ancillary PPARγ activity and documented favorable impact on risk for vascular events, in "polypills" designed for health protection in the general population, may be envisioned. Indeed, Wald *et al.* [310] have recently proposed a polypill containing 25 mg losartan per daily dose. A major proviso is that ARB must be discontinued with the onset of pregnancy, as ARB are toxic to fetuses, particularly during later pregnancy [311,312]. Such a strategy may not be feasible in some individuals who are hypotensive or borderline hypotensive, and it must be borne in mind that hypotension can pose a significant health risk in the elderly, as it may increase risk for falls and impair brain perfusion in those with poor autoregulatory control [313,314]. With respect to telmisartan, it should be noted that, in rodent studies, this agent has a favorable impact on maintenance of bone density, and even antagonizes the adverse effect of rosiglitazone in this regard [315,316]; hence, telmisartan may not have the detrimental effect on bone health that is seen with thiazolidinedione PPARγ agonists [317-319]. Full agonists for PPARγ such as thiazolidinediones bind to this receptor in such a way as to enable the dephosphorylation of Ser112 and Ser273, necessary for the full transcriptional activity of PPARγ. The binding of telmisartan, however, only enables

the dephosphorylation of Ser273; this effect is sufficient for the insulin-sensitizing, anti-inflammatory effects of PPARγ, but insufficient for its adipogenic and anti-osteoblastic actions [319]. Hence, while not as strong an insulin-sensitizing agent as thiazolidinediones, the PPARγ-mediated effects of telmisartan are more uniformly positive; the favorable impact of telmisartan on bone in rosiglitazone-treated rats presumably reflects its ability to compete with rosiglitazone for binding to PPARγ, preventing this drug from promoting Ser112 dephosphorylation. With respect to other ARB, some studies [320,321], though not others [322,323], suggest that ARB as a class may have a favorably influence bone density or fracture risk.

A second implication is that other source antioxidants may have tremendous health protective potential. The superior health outcomes associated prospectively with elevated bilirubin levels may demonstrate the merit of down-regulating Nox activity systemically. This protection should be complementary to that afforded by angiotensin antagonist drugs, as Nox can be activated in many tissues in which the RAS has minimal activity; moreover, even in tissues that do express AT1R, additional factors may promote Nox activation, e.g. oxidized low-density lipoprotein, hyperglycemia, elevated free fatty acids, and endothelin in vascular endothelium [324-326]. Conversely, it is not yet clear whether bilirubin can inhibit all of the forms of Nox, which AT1R can activate.

Although the insolubility of bilirubin and the lack of rich natural sources of its more soluble precursor biliverdin limit the clinical practicality of these agents, it is notable that food cyanobacteria such as spirulina contain high amounts (about 0.6% by dry weight) of a chromophore, phycocyanobilin (PhyCB), that is a biliverdin metabolite and shares the capacity of biliverdin/bilirubin to inhibit Nox [327,328]. This likely explains why, in rodents studies, oral administration of spirulina, phycocyanin (the spirulina holoprotein containing PhyCB), or of free PhyCB has been shown to oppose atherogenesis, suppress diabetic nephropathy, prevent onset of diabetes, ameliorate fatty liver disease, and slow the progression of neurodegeneration in models of PD and dementia [328-337], effects parallel to those reported for angiotensin antagonist drugs, in addition to providing protection in various models of inflammatory disorders [338]. Unfortunately, with the exception of a study from Cameroon concluding that spirulina (19 g daily) can markedly improve insulin sensitivity in HIV patients with protease inhibitor-induced insulin resistance [339], there so far have been few controlled clinical trials evaluating ample intakes of spirulina or of PhyCB-enriched spirulina extracts. Evidently, the clinical potential of spirulina/PhyCB should receive serious research attention.

It is increasingly clear that Nox activation plays a mediating or exacerbating role in a very wide range of pathologies [340]. In these disorders, if the affected tissues express AT1R and other components of the RAS system, endogenous AT1R activity, via joint stimulation of PKC and Rac, can be expected to boost Nox activity; conversely, angiotensin antagonist drugs could be expected to down-regulate this activity, whether or not the disorder entails an increase of AT1R activation, though more notably if it does. The combined administration of angiotensin antagonist drugs and a direct inhibitor of Nox complexes, such as PhyCB, might be expected to have an especially potent impact on the contribution of Nox-generated oxidative stress to disease pathogenesis. In particular, joint administration of telmisartan and adequate amounts of spirulina/PhyCB, as a preventive health measure, might be expected to unite a profound systemic antioxidant activity, blood pressure reduction and the metabolic benefits of PPARγ agonism, with minimal risk for side-effects.

It should be noted that statin therapy also has the potential to down-regulate Nox activity systemically, by impeding the isoprenylation of Rac required for its membrane translocation [341-345]. While this phenomenon is readily demonstrated in rodent and cell culture studies, the extent to which it contributes to the protection afforded by clinically tolerable doses of statins remains unclear; nonetheless, it is suspected to contribute to the anti-inflammatory impacts of these drugs. The fact that joint use of statins and angiotensin antagonists was found to have the largest impact on mortality in COPD is suggestive of a complementary effect of these drugs on Nox activity [151].

Other nutrients or drugs can function as source antioxidants by targeting other sources of superoxide. In dysfunctional endothelium in which eNOS is "uncoupled" by oxidative stress, and becomes a generator of superoxide, high-dose folic acid can act as a source antioxidant by preventing or reversing peroxynitrite-mediated oxidation of the cofactor tetrahydrobiopterin, effectively "recoupling" eNOS so that is no longer produces superoxide [346-348]. This reflects the ability of the reduced folate metabolites produced intracellularly to scavenge peroxynitrite-derived radicals [349]. In the context of ischemia-reperfusion, astaxanthin can function as a source antioxidant by minimizing oxidative damage to the mitochondrial respiratory chain during ischemia, thereby reducing the propensity of mitochondria to over-produce superoxide when oxygenation is restored [350-353]. With respect to xanthine oxidase, a structurally altered form of xanthine dehydrogenase that produces superoxide, the gout drug allopurinol serves as a source antioxidant by direct inhibition of the enzyme; this may rationalize reports that allopurinol therapy can improve the function of vascular endothelium in heart failure patients, provide symptomatic benefit in angina, and reduce left ventricular mass in patients with cardiac ischemia [354-356].

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