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L. J. JANSSEN [2005] MED HYPOTHESES RES 2: 525-532.

**ISOPROSTANES: NOT JUST MARKERS,
BUT ALSO CATALYSTS OF
ALZHEIMER'S DISEASE?**

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REVIEW

ABSTRACT. ALZHEIMER'S DISEASE (AD) has been studied for decades, and yet its etiology is still poorly understood. Several factors have come to be associated with AD, including neurofibrillary tangles (comprised largely of β -amyloid peptides), metal ions, and defects in cerebrovascular perfusion. However, the links between these factors, if any, are unclear. More recently, isoprostanes have also come to be strongly associated with AD and animal models of AD. Isoprostanes are not only markers of oxidative stress, but are now increasingly recognized as being able to exert important biological effects including powerful vasoconstriction. Here, we propose a novel hypothesis in which isoprostanes bring together the factors identified above, and, thus, may play a central role in the development of AD.

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1. ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the most prevalent cause of dementia with ageing. Its manifestation is insidious and progressive, increasing with chronological age such that half of the population over the age of 80 is vulnerable [8]. The major clinical deficit which heralds the disease is a pronounced and progressive loss of memory. The precise neuropathological mechanisms underlying this disease are still unclear, despite decades of research. However, several factors have now been closely linked to the development of AD. The latter has long been associated with the presence of amyloid plaques in which there is marked accumulation of β -amyloid (A β) peptides [19], as well as various metal ions. More recent studies have shown AD to be associated with defects in cerebral perfusion (SECTION 2) and the production of free radicals and isoprostanes (SECTION 3). However, the relationships among these various factors are unknown. In this review, we propose a novel and testable hypothesis which brings together these 5 factors into the pathophysiology underlying AD (SECTION 5).

2. ISOPROSTANES: OXIDATIVE LIPID METABOLITES

Oxygen-centered radicals such as peroxide and superoxide are present in a wide variety of disease states, and, in fact, may play important roles in the pathophysiology underlying those diseases [29,64,66]. These reactive oxygen species (ROSs) can oxidize peptides and polyunsaturated fatty acids (either in free form or while still esterified within the lipid membrane), leading to the formation of a wide variety of breakdown products. One major group of these products which are attracting a great deal of attention are collectively referred to as isoprostanes: these comprise a cyclopentane ring with two alkyl chains *cis* to one another. As such, these are isomeric with cyclooxygenase-generated prostanoids (hence the name "isoprostanes"), which have the two side chains *trans* to one another. An-

other important difference between the isoprostanes and the prostanoids is that, while the latter are generated enzymatically only after their parent molecule, arachidonic acid, has been liberated from the membrane by phospholipase activity, free radicals can interact with polyunsaturated fatty acids while they are still esterified within the membrane: this point will become particularly relevant below (SECTION 4). Isoprostanes have been detected at nanomolar concentrations in serum and blood of normal individuals [9,10,43,49,63] and their concentrations are further increased several orders of magnitude in many disease states characterized in part by oxidative stress (see SECTION 2). While their relative stability has made isoprostanes particularly valuable as markers of oxidative stress as well as disease state and severity, the possibility that they may actually play a causal role in the pathophysiology of disease has not yet been considered carefully.

3. IS THERE A CONNECTION BETWEEN ALZHEIMER'S DISEASE AND ISOPROSTANES?

Many studies have documented a dramatic elevation in the levels of isoprostanes and their metabolites in the cerebrospinal fluid and brain tissues of patients with AD [2,18,22,40-42,50-52,56,61,68]. It should be pointed out that these measurements likely underestimate the local concentrations attained at the actual site of generation of these compounds, since they reflect only the average concentration of free or de-esterified isoprostanes. More importantly, the levels of isoprostanes correlate with various measures of disease severity (cognitive and functional impairment, cerebrospinal fluid tau and amyloid, and number of ApoE ϵ 4 alleles) [50,51].

Animal models of AD also correlate with isoprostane production. For example, in a transgenic mouse model (Tg2576) of AD amyloidosis, isoprostanes began to accumulate in urine, plasma, and brain tissues prior to appearance of amyloid plaques [54]. Mice which lack apolipoprotein E (ApoE) exhibited neurodegenerative changes accompanied by accumulation of isoprostanes in

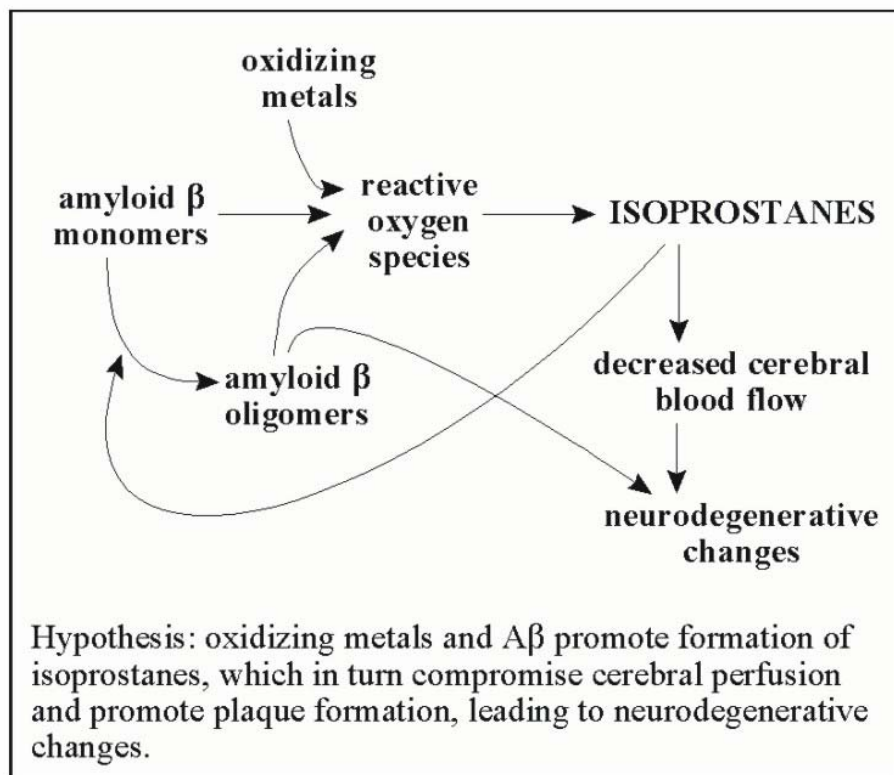


FIGURE 1. SCHEMATIC REPRESENTATION OF THE PROPOSED HYPOTHESIS.

the brain [53]. A more recent study comparing ApoE-deficient and ApoE-transgenic mice found changes in isoprostane levels mirrored those of A β peptides [67]. In mice that were made to overexpress human A β precursor protein, ingestion of oxidizing metals led to increased levels of isoprostanes, the magnitude of which correlated with the increased levels of A β in the brain and accelerated plaque deposition [55]; all of these effects were reversed by vitamin E (a free radical scavenger) [55]. Likewise, in another animal model of AD, the antioxidant curcumin significantly reduced the increased levels of isoprostanes as well as the structural changes (A β deposition, loss of synaptophysin; reduced postsynaptic density) and functional changes (memory loss) brought on by infusion of A β [14].

A β peptides and oxidizing metals are both associated with AD. However, the role(s) that they

may play in the development of AD, if any, have not yet been resolved. Both can promote the formation of free radicals (and therefore also isoprostanes). The methionine group at residue 35 of the A β peptide seems to be particularly important in this respect [20]. A β peptides bind copper ions with high affinity and can influence the Fenton chemistry of this metal, thereby operating as a pro-oxidant. The protective or deleterious effects of the ApoE isotypes in AD parallels their abilities to act as antioxidants (ApoE ϵ 2 > ApoE ϵ 3 > ApoE ϵ 4). Finally, isoprostane production induced by Ca²⁺ ionophore (which activates phospholipase A₂) was measured in brain synaptosomes prepared from rats of varying ages: this was uniform between age groups, but increased dramatically in an age-dependent fashion in tissues preincubated with A β peptides [6,7].

4. IS THERE A CONNECTION BETWEEN AD AND VASCULAR CHANGES?

Many have shown cerebral blood flow to be decreased in AD patients [26,34,44,57,58]; in fact, many believe that any condition which compromises cerebral blood flow predisposes an individual to AD [12]. Cerebral hypoperfusion leads to cortical watershed microinfarcts, which can aggravate the neurodegenerative process and increase dementia [59]. In mice which overexpress A β precursor protein, cerebrovascular autoregulation (the ability to maintain cerebral blood flow in the face of altered systemic blood pressures) is markedly impaired [45]. Also, direct application of A β reduces cerebral blood flow and augments the vasoconstrictor responses to the thromboxane mimetic U46619 [46] or to endothelin [48]: one important observation which greatly underscores our hypothesis in this proposal is that these effects are abrogated when a single methionine within the applied A β peptides is substituted with norleucine, a mutation which abolishes their ability to produce free radicals [46]. This vasoconstrictor effect of A β protein is sensitive to inhibitors of cyclooxygenase or lipoxygenase (which can also represent a potent source of reactive oxygen species) or of phospholipase (which can liberate isoprostanes esterified within the plasmalemma) [48]. Others [57] have shown a correlation within probable AD patients between the presence of the ApoE 4 allele (which is less protective against ROS) and reduced cerebral blood flow.

5. BIOLOGICAL ACTIONS OF ISOPROSTANES

While they are indeed useful as markers of oxidative stress and disease state, there is now extensive evidence that isoprostanes are also mediators of a variety of biological effects (reviewed in ref. [23]) and may therefore play a causal role in those diseases. Concurrent with discovering 8-iso PGF_{2 α} in human plasma and urine, the group led by Drs. Morrow and Roberts also examined its effects on renal vascular function, finding it to powerfully and potently reduce renal blood flow

and glomerular filtration rate [43]. Since that initial report, 8-iso PGF_{2 ν} in particular has been shown to elicit excitatory responses in virtually every vascular smooth muscle in which it has been tested, including the cerebral [21], pial [21], aortic [31,65], carotid [39], coronary [30,38], pulmonary [1,27,28], renal [16,43,60], portal [35], umbilical [47], and retinal [32,37] vasculature. There is also recent evidence that certain isoprostane molecules may be important as vasodilators [24].

In general, these excitatory effects of isoprostanes appear to be exerted through prostanoid receptors which are selective for thromboxane A₂ (referred to as TP receptors) [23]. More recently, some have described responses via other prostanoid receptors, including those which are selective for prostaglandin E₂ (EP receptors) [13,25,62], and prostaglandin F_{2 α} [62]. This cross-reactivity should not be surprising given the many structural similarities between prostanoids and isoprostanes. Others have suggested the possible existence of a novel group of isoprostane-selective receptors [15,17,33].

On the other hand, isoprostane-mediated effects may also involve chemical modification of membrane proteins [2]. Ring cleavage of E-ring isoprostanes and prostanoids liberates reactive molecules with a (-keto aldehyde functional group which easily and rapidly forms adducts with amine groups [3,4]. More importantly, the initial lysyl-adducts of this reaction are also highly reactive, leading to extensive intermolecular cross-linking [2-5]. Furthermore, adduction of isoprostane-derived ketal groups to proteins/peptides markedly impairs the ability of proteasomes to degrade and process those substrates [11]. Thus, there may be a self-reinforcing cycle of isoprostane and A β peptide formation, each perpetuating or promoting the synthesis of the other.

6. HYPOTHESIS: ISOPROSTANES PLAY A KEY ROLE IN THE DEVELOPMENT OF AD

Although there is growing evidence for A β peptides, oxidizing metals, and altered cerebral

blood flow as causal factors in the pathogenesis of AD, the links between these are still quite unclear. We propose the novel hypothesis that isoprostanes may represent a crucial link between them, as summarized in FIG. 1. Metals and A β peptides have both been shown to catalyze the formation of reactive oxygen species including peroxide and superoxide (SECTION 2), which in turn cause formation of isoprostanes (SECTION 1). At the same time, isoprostanes can form lysyl-adducts with proteins and thereby promote intermolecular cross-linking (SECTION 4). This becomes a particularly important point in light of the fact that isoprostane formation does not first require release of the parent polyunsaturated fatty acid molecules, but can occur while the latter are still esterified within the membrane. Thus, isoprostanes so produced can be sequestered at the site of initial free radical formation and set the stage for a perpetuating accumulation of A β peptides and other isoprostanes, and be slowly released from the site of injury, in the vicinity of the cerebral vasculature. This sequestration of the isoprostanes to sites where A β peptides have seeded could explain why other neurodegenerative diseases which also associated with isoprostane formation (e.g., Huntington's disease) produce different clinical features than those seen in AD. Isoprostanes are potent constrictors in many vascular beds (SECTION 4), thus accounting for the compromised cerebral blood flow and subsequent neurodegenerative changes seen in AD (SECTION 3). Consistent with the latter point, isoprostane accumulation precedes plaque formation [54,67].

7. CONCLUSION

A potential causal role for isoprostanes in AD, although compelling on the basis of the arguments outlined above, requires a great deal more study. First, the interactions between A β peptides, oxidizing metals and isoprostanes needs to be scrutinized more closely. Also, the effects of isoprostanes on cerebral vasculature are poorly understood: there has been only one study, using only two isoprostane isomers, done in the mouse cerebral and

pial vasculature [21]. Many examples are documented in which the responsiveness to isoprostanes can vary in a compound- and species-related fashion [23]. Moreover, that one study done in murine vasculature [21] did not investigate the mechanisms underlying the isoprostane-evoked responses, particularly the receptors involved. Identification of the latter could lead to novel approaches for the treatment, or even prevention, of AD. Alternatively, it may be possible to achieve this goal using antioxidants to prevent the formation of isoprostanes: consistent with this, some (but not all) clinical studies suggest that antioxidants may be useful in the treatment of AD [36]. Any agents or interventions used for this purpose must be able to cross the blood brain barrier and to gain access to the putative site of isoprostane production (those areas in which the β -amyloid peptides and metal ions are localized).

ACKNOWLEDGMENTS

We acknowledge the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada, and the Ontario Thoracic Society in their support of our studies of isoprostane biology.

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RECEIVED ON 6-20-2005.

ACCEPTED ON 6-28-2005.