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Biomarkers for Cognitive Aging Part II: Oxidative Stress, Cognitive Assessments, and Medication Adherence

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Abstract

The purpose of this study was to further examine potential biomarkers of cognitive aging by looking at the associations among oxidative stress, cognitive abilities, and medication adherence in a community-based sample of middle-aged and older adults ($n = 42$; mean age = 69 years) prescribed at least one medication for hypertension. In addition to measures described in Part I, "Biomarkers for Cognitive Aging," a 12-hr urine collection for F_2-isoprostanes served as an indicator of oxidative stress. Participants completed a battery of cognitive assessments and 8 weeks of electronic medication monitoring for adherence to one antihypertensive agent. Oxidative stress was significantly associated with logical memory, immediate ($r = -.38$, $p < .01$) and delayed recall ($r = -.42$, $p < .01$), and recognition memory ($r = -.42$, $p < .01$) from the Wechsler Memory Scale III, number of perseveration errors ($r = .26$, $p < .05$) and categories achieved ($r = -.26$, $p < .01$) on the Wisconsin Card Sorting Test (WSCT), and medication adherence ($r = -.34$, $p < .05$). Findings indicate that a biomarker of oxidative stress, F_2-isoprostanes corrected for vitamin E, is significantly associated with cognitive measures and a functional outcome.

Keywords

oxidative stress, cognition, adherence, hypertension

Aging is associated with declines in particular cognitive processes that are associated with functional outcomes (Insel, Morrow, Brewer, & Figueredo, 2006; Royall, Cabello, & Polk, 1998; Royall, Cordes, & Polk, 1997; Royall, Palmer, Chiodo, & Polk, 2004, 2005; Stilley, Bender, Dunbar-Jacob, Sereika, & Ryan, 2010). While cognitive aging is associated with functional outcomes, less well understood are the biological mechanisms that underlie cognitive aging. Oxidative stress and the theory of free radicals is one of the leading theories of aging. If oxidative stress is associated with cognitive processes and with a functional outcome, then it is possible that interventions directed toward minimizing or preventing oxidative stress would limit consequent functional decline. Such interventions could lead to improved quality of life while lowering the costs of caring for our expanding elderly population. In the current study, we sought to examine the associations among oxidative stress, performance on selected age-sensitive cognitive assessments and a functional outcome, in this case adherence to prescribed hypertension medication, in a sample of community-dwelling middle-aged and older adults with hypertension.

Background

Oxidative stress occurs when the production of free radicals, or reactive oxygen species (ROS), exceeds the level of cellular antioxidant defenses that function to neutralize the free radical formation (Droge & Schipper, 2007; Greco & Minghetti, 2004). Free radicals are highly reactive molecules with an unpaired electron capable of easily reacting with other molecules. Common ROS are the superoxide anion ($\bullet O_2^-$) and the hydroxyl radical ($\bullet OH$; Halliwell & Grootveld, 1987). Hydrogen peroxide (H_2O_2), while technically not a free radical, forms the more reactive hydroxyl radical when exposed to ultraviolet light (Halliwell, Clement, & Long, 2000) or, potentially more relevant to cognitive aging, to iron salts as in the Fenton reaction (Halliwell & Chirico, 1993).

Free radicals form naturally during intracellular respiration in the mitochondria (Floyd, 1999) and are necessary for cell signaling (Halliwell et al., 2000; Touyz, 2003) and other important functions (Vaziri, 2008). An overabundance of free radicals is known to cause damage to DNA, proteins, and lipids, often leading to programmed cell death, or apoptosis (Chan, 2001). Therefore, cells closely regulate free radicals

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with enzymes that neutralize them, such as superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase, and with other antioxidants, such as ascorbic acid (vitamin C), and alpha tocopherol (vitamin E; Chan, 2001; Touyz, 2003; Vaziri, 2008).

The causes of cognitive decline with older age are not clear, but there is some support for oxidative damage as a causal factor in brain aging. This evidence is complemented by findings suggesting that antioxidants in the diet have a protective effect for cognitive function (Berr, Balansard, Arnaud, Roussel, & Alperovitch, 2000; Berr, Richard, Roussel, & Bonithon-Kopp, 1998). We do know that the brain is particularly vulnerable to oxidative damage because of the high concentration of lipids; the presence of transition metals, which can produce reactive oxygen species; low antioxidant activity; and high metabolic activity (Floyd, 1999; Qureshi, Baig, Sarwar, & Parvez, 2004; Reynolds, Laurie, Mosley, & Gendelman, 2007). There is also evidence that synaptic sites are vulnerable to oxidative stress (Onodera et al., 2003). Therefore, examining the associations among oxidative stress, cognitive performance, and a functional outcome could yield important new information for subsequent studies investigating the use of dietary antioxidants to maintain functional status among older adults.

Method

Sample and Setting

The sample and setting are the same as described in Part I, "Biomarkers for Cognitive Aging." We screened participants for dementia using the Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and for depression using the Short Form of the Geriatric Depression Scale (GDS-15; Fountoulakis et al., 1999).

Procedure

Following a formal consent procedure and screening for dementia and depression, we obtained two seated blood pressure (BP) measures 5 min apart with a digital BP device (Omron HEM 739, Omron Healthcare, Inc. Bannockburn, Illinois). We drew blood for the vitamin E assay, obtained demographic information, and administered the cognitive assessments. Participants transferred one prescribed antihypertensive agent to a medication electronic monitoring system (MEMS; Aardex Group, 2002) as described in Part I. We asked participants to begin a 12-hr urine collection on the evening that we collected the other data. We provided them each with a urine collection container and instructed them to begin collecting urine at approximately 7:30 p.m. The following morning we picked up the urine and brought it to the laboratory where we measured and stored it at -80°C to prevent any possible degradation of the isoprostanes before analysis at a later date. We collected the MEMS cap 8 weeks after the initial data collection.

Measures

Demographic data, cognitive assessments, and BP. Demographic, cognitive, and BP measures are described in Part I.

Vitamin E measurement. We sent serum obtained from the blood samples to ARUP Laboratories (Salt Lake City, Utah) to obtain alpha-tocopherol levels by high-performance liquid chromatography. Alpha-tocopherol was the measure of vitamin E we used in this study.

Isoprostane and creatinine assays. Use of isoprostanes as a measure of oxidative stress is a common approach because isoprostanes are end products of lipid peroxidation and more stable then direct measures of free radicals. Free radicals are transient and unstable molecules that easily react with other molecules in the cell. Isoprostanes are prostaglandin isomers produced when free radicals damage arachidonic acid (Morrow, 2005), a lipid found in the brain (Cracowski & Durand, 2006; Morrow, 2000). Lipid peroxidation is considered to be a late event in the cascade of oxidative damage, accompanying cell death (Halliwell & Chirico, 1993). Some investigators have concluded that the best marker of oxidative stress is the measurement of isoprostanes in urine and plasma (Young, 2005) because it is specific for lipid peroxidation, reliable, and noninvasive (Roberts & Morrow, 2000). Furthermore, urine F_2-isoprostane levels should reflect oxidative metabolism in the body (Greco & Minghetti, 2004).

We treated the 12-hr urine sample with the commercially available Glucuronidase Sample Treatment Kit (Oxford Biomedical Research, Oxford, Michigan). We measured isoprostanes from the urine using a commercially available ELISA kit (Urinary Isoprostane Assay Kit, Oxford Biomedical Research, Oxford, Michigan). In order to correct for volume, we measured creatinine by the Jaffé picric acid method using a commercially available kit (Creatinine Assay kit, Oxford Biomedical Research, Oxford, Michigan). We corrected the level of isoprostanes for creatinine.

Medication adherence. As indicated in Part I, we measured medication adherence over 8 weeks to the interdose interval for one of the participant's prescribed antihypertensive agents using the MEMS. If the participant was taking more than one prescribed antihypertensive medication, we randomly determined which one to monitor.

Results

Demographic Variables

Part I describes characteristics of the sample. In addition, mean number of minutes engaged in exercise each week was 50.27 with a range of 0-120 min per week.

Table 1. Mean, Standard Error, and Range for the Cognitive Variables and Indicators of Oxidative Stress for Participants ($N = 42$)

Measure	*M* (*SE*)	Range
WMS immediate total recall	17.12 (1.25)	4–33
WMS long-delay total recall	15.88 (1.28)	3–34
WMS recognition	23.0 (0.615)	15–30
WCST categories completed	2.02 (0.24)	0–5
WCST perseveration errors	46.45 (2.35)	20–80
Isoprostane level (ng/mL)	3.29 (0.28)	1.3–10.1
Creatinine level (mg/dL)	90.27 (7.38)	30.5–243.5
Index of oxidative stress[a]	0.295 (0.03)	0.07–0.88
Alpha-tocopherol (vitamin E; units)	13.96 (0.84)	5.0–35.9

Note: WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale.
[a] Index of oxidative stress = the ratio of isoprostanes per mg of creatinine/vitamin E.

Cognitive Measures

Table 1 presents the mean, standard error, and range of the scores for immediate and delayed recall and recognition memory and Wisconsin Card Sorting Test (WCST) categories completed and perseveration errors. The cognitive measures included in the table were associated with oxidative stress in the present study.

Oxidative Stress Measures

The oxidative stress index that we used was the ratio of isoprostanes per milligram of creatinine/vitamin E, according to the method Epel and colleagues (2004) reported. The index of oxidative stress and alpha-tocopherol (vitamin E) levels also appear in Table 1. The normal range of alpha-tocopherol levels is 5.5–18.0 mg/L. The mean of our sample was in the mid to high end of the normal range (13.96 mg/L).

Correlations

Table 2 presents the correlations among study variables. Oxidative stress was significantly and inversely associated with education, exercise, immediate and delayed recall and recognition, categories achieved from the WCST, and adherence. We also found positive associations between oxidative stress and perseveration errors on the WCST and financial well-being, with finances coded such that the higher number reflects a lower sense of financial well-being. Oxidative stress was not associated with telomere length in this sample.

Letter Number Sequence and Mental Control were not significantly associated with oxidative stress ($r = -.20$ and $r = -.19$, respectively). Letter Number Sequence and Mental Control were associated with medication adherence in the anticipated direction ($r = .33, p < .05$ and $r = .29, p < .05$, respectively).

Education was significantly associated with each of the cognitive measures in the anticipated direction and inversely associated with mean systolic BP (SBP) and financial well-being, as expected, as well as with oxidative stress. In this sample, education predicted medication adherence. Using education as a covariate, we calculated a linear regression to examine the influence of oxidative stress on adherence. When controlling for education, oxidative stress was no longer a significant predictor of adherence although the association remains close to significant ($\beta = -.28, p = .06$).

SBP was significantly associated with many of the cognitive measures; however, it was not significantly associated with perseveration on the WCST or oxidative stress, although the association between SBP and oxidative stress approached significance ($r = .25, p = .052$). In this study, two averaged SBP measures were not significantly associated with a current measure of oxidative stress. Oxidative stress may be a better overall indicator of cognitive function compared to BP taken at one point in time.

We examined the effects of ancestry/ethnicity using a one-way ANOVA with ethnicity as the grouping variable and oxidative stress as the outcome ($F = 7.65, p < .01$). Using a Bonferroni correction to examine the effects of group, we found the significant differences on oxidative stress to be between Caucasians and individuals of Hispanic heritage. Caucasians had lower measures of oxidative stress compared to persons of Hispanic heritage (mean difference $= -.25268, p < .01$).

Discussion

Oxidative damage can occur in the cell through either an increase in the production of ROS or an accumulation of oxidized lipids, proteins, and nucleic acids. We sought to examine the association of oxidative stress with age-sensitive measures of cognitive function that would also be associated with a functional outcome, that of adhering to a prescribed medication. It is well known that there is a high level of variability in cognitive ability among middle- and old-aged adults. We reasoned that a biomarker might be useful for understanding individual capacity for self-management if the biomarker was also associated with adherence. In this study, oxidative stress appears to be a robust indicator of age-sensitive measures of cognitive function and, importantly, of taking medication as prescribed.

Others have examined the role of oxidative stress and its potential importance as a biomarker of cognitive aging and even as a precursor of cognitive decline (for reviews see Droge & Schipper, 2007; Foster, 2006). In a longitudinal study, scores on the MMSE (Folstein et al., 1975) were associated with plasma levels of thiobarbituric acid reactant substances (TBARS), an indicator of lipoperoxidation (Berr et al., 2000). Investigators defined cognitive decline as a loss of 3 points on the MMSE between baseline and the 4-year follow-up assessment. Those with the highest level of TBARS demonstrated increased risk of cognitive decline (adjusted odds ratio = 2.25). The authors concluded that high levels of oxidative stress and/or antioxidant deficiencies could pose a risk for cognitive decline. The MMSE is a global measure of cognition, and decline on this measure may herald pathological changes associated with dementia rather than age-associated cognitive decline. The findings from Berr and colleagues may not converge with studies looking at associations between oxidative stress and cognitive assessments that are sensitive to

Table 2. Zero Order Correlations Among Oxidative Stress, Cognitive Measures, Exercise, Financial Well-being, Education, and Medication Adherence

Variables	Ox Stress	Edu	MSBP	Exer	Fin	WMS Recall	WMS Delayed Recall	WMS RCG	WCST PE	WCST CC	Adherence
Edu	−.36**										
MSBP	.25	−.40**									
Exercise	−.32*	.41**	−.32*								
Finances	.32*	−.69**	.23	-.43**							
WMS Recall	−.38**	.61**	−.37**	.41**	−.50**						
WMS Delayed Recall	−.42**	.58**	−.47**	.37*	−.45**	.93**					
WMS RCG	−.42**	.49**	−.32*	.36*	−.36*	.84**	.84**				
WCST PE	.26*	−.37**	.24	−.30*	.42**	−.47**	−.45**	−.48**			
WCST CC	−.26*	.48**	−.38**	.23	−.48**	.71**	.70**	.61**	−.71**		
Adherence	−.39*	.41**	−.34*	.06	−.29**	.35*	.32*	.19	−.21	.28*	
A VE	−.52**	.39**	−.18	.22	−.20	.42**	.42**	.57**	.04	.12	.35*

Note. A VE = alpha-tocopherol (measure of vitamin E); Adherence = % of doses taken on schedule; CC WCST = categories completed WCST; Edu = self-reported achieved educational level; Exer = amount of exercise (in min per week); Fin = financial well-being, with higher numbers reflecting a lower sense of well-being; MSBP = mean systolic blood pressure; Ox Stress = oxidative stress index; PE WCST = perseveration errors WCST; WCST = Wisconsin Card-Sorting Test; WMS III = Wechsler Memory Scale;WMS Delayed Recall = WMS III total recall, delayed; WMS RCG = WMS III recognition score; WMS Recall = WMS III immediate total recall.

* $p < .05$.

** $p < .01$.

age-related cognitive processes. Berr's study also did not find an association between vitamin E and cognitive decline. They speculate that vitamin E levels in red blood cells may not correlate well with plasma levels of vitamin E. Importantly, the Berr study was the first to demonstrate that high levels of lipoperoxidation were associated with cognitive decline.

Oxidative Stress and Cognition

In the current study, we found that oxidative stress was correlated in the expected directions with measures of age-sensitive cognitive processes, medication taking behavior, self-reported engagement in exercise, levels of financial strain, and vitamin E. This evidence, the first to our knowledge to associate oxidative stress and a functional outcome, in other ways converges with an increasing number of empirical reports suggesting that oxidative stress is correlated with cognitive function and that the presence of antioxidants and engagement in exercise may attenuate the deleterious effects of oxidative stress on the cell. Importantly, we calculated the index of oxidative stress used in this study by correcting for vitamin E.

There is additional evidence that antioxidants can prevent cognitive decline. Several studies have associated the presence of antioxidants with performance on cognitive measures. Data from the European Vascular Aging population-based study showed that low levels of carotenoids (an antioxidant) were associated with lower scores on the Digit Symbol Substitution (from the Wechsler Adult Intelligence Scale—R) and Trail-Making Test part B, although this relationship did not hold with other measured antioxidants (Berr et al., 1998). The criteria used for cuts-offs for low cognitive performance and low antioxidant levels was <25th percentile, which fails to capitalize on the continuous nature of these variables and may result in loss of power to detect an association between cognitive performance and antioxidant levels.

As early as 1996, Snowdon, Gross, and Butler observed an inverse relationship between the antioxidant lycopene and functional outcomes such as dependence in self-care. They did not find a statistically significant association between alpha tocopherol and self-care; however, with increases in lycopene, total carotenoids, and alpha tocopherol, there was a decrease in overall dependency in self-care. They defined dependence in self-care as need for assistance with activities of daily living (ADLs) including assistance with bathing, walking, dressing, standing, toileting, and feeding. In the current investigation, alpha tocopherol was associated with an instrumental activity of daily living, medication adherence. Medication adherence requires higher cognitive processes than performing ADLs. It may be associated with the presence of other antioxidants, such as lycopene, that were not investigated in the current study.

Alpha tocopherol was significantly and inversely associated with oxidative stress and positively associated with education, measures of recall and recognition, and taking medications as prescribed in the current study, suggesting that the more educated the sample the greater the likelihood that participants have a rich and varied diet with adequate intake of vitamin E. However, we did not assess dietary intake of vitamin E, and further investigation is needed.

Perkins and colleagues (1999) examined serum levels of several antioxidants, including vitamins E, C, and A, carotenoids, and selenium, in a cohort of elderly individuals in the Third National Health and Nutrition Examination study. The findings indicated that elderly individuals with high levels of vitamin E had better memory function after controlling for age, education, income, vascular risk factors, and other trace elements. None of the other measured antioxidants was associated

with better memory performance. The memory measure did not assess age-associated cognitive processes, and the findings point to potential prevention of dementia rather than the prevention of age-associated cognitive decline.

Using a canine animal model, Cotman, Head, Muggenburg, Zicker, and Milgram (2002) were able to establish a link between cognitive decline and oxidative stress. They then tested a dietary intervention to examine the effect of antioxidants on cognitive function. They supplemented the canine diet with vitamins E and C, a mixture of fruits and vegetables, alpha-lipoic acid, and L-carnitine (mitrochondrial cofactors), selecting the supplements based on declines in measures of oxidative stress in serum and urine following dietary supplementation. Young canines showed no improvement with the dietary supplementation, but older canines demonstrated improvement on the more difficult cognitive tasks. The authors caution that many of the antioxidants also have anti-inflammatory properties. It could be that, in brains where both oxidative stress and inflammation were present—as may have been the case for many of the older canines—there were two mechanisms responsible for the improvement in cognitive performance: the hypothesized pathway of oxidative stress and an anti-inflammatory pathway.

More recently, Jolitha, Subramanyam, and Ashi Devi (2009) showed improvement in T-maze learning connected to the cholinergic system in aged rats with interventions of both vitamin E and exercise. The effect of the antioxidants may include influences on the cholinergic system. The authors speculated that vitamin E and exercise may have the functional outcome of inhibiting acetylcholine esterase, which then is used in upregulating acetylcholine for older adults with memory deficits (for a review see Asha Devi, 2009).

The robust associations between attained educational level and measures of cognition, SBP, oxidative stress, and adherence that we found in the present study are interesting. In this sample, educational level may be a proxy variable indicating improved self-management using prescribed antihypertensive agents, which in turn shows beneficial effects on important clinical outcomes including cognitive function and oxidative stress. Education was also correlated with more exercise, which can lower levels of oxidative stress. Education may be an important moderator in the association between oxidative stress and cognitive outcomes.

Ancestry/ethnicity was associated with levels of oxidative stress in our sample. Specifically, Caucasians demonstrated lower levels of oxidative stress than individuals of Hispanic heritage. It is possible that polymorphisms involved in oxidative stress pathways are responsible for these findings. It is also possible that there are differences in these populations in regards to nutrition and exercise giving rise to differences in levels of oxidative stress. Whether the explanation is genetic or a consequence of health disparities remains to be discovered and is an area for further research.

Limitations

Hypertension involves a progressive cycle of increased oxidative stress and deterioration of the endothelium. The presence of hypertension accelerates the rate of biological aging (Fuster, Diez, & Andres, 2007). Furthermore, cognitive decline is associated with the severity of hypertension (de Leeuw et al., 2002). In the present sample, hypertension may be the primary causal factor. In other words, because the sample was composed of middle- and old-aged adults with hypertension, it may be that hypertension influenced both oxidative stress and cognitive ability.

Another potential limitation is our choice of measures for oxidative stress. We measured F_2-isoprostanes in urine as an overall measure of systemic oxidative stress and assumed that it would reflect oxidative stress in the brain. While systemic measures of oxidative stress may reflect oxidative stress in the brain, these measures are not direct indicators of the levels of oxidative stress centrally because of the blood–brain barrier.

Implications for Future Research

Further investigation is warranted into the specific benefits of antioxidants and exercise and the co-occurring levels of oxidative stress among humans. The associations that we found in the present study indicate that education is also correlated with exercise, financial well-being, and vitamin E levels. Education may have a modifying role by influencing lifestyle factors that protect the individual against the cognitive decline associated with hypertension. The associations among oxidative stress, cognitive assessments, and functional outcomes is also worthy of further examination. If functional decline can be delayed or prevented through use of interventions such as antioxidants and exercise, the findings have implications for both individuals and society as a whole.

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