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Review article

Oxidative stress and cognition amongst adults without dementia or stroke: Implications for mechanistic and therapeutic research in psychiatric disorders

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ABSTRACT

Oxidative stress has been implicated in cognitive deficits in disease states such as dementia and stroke. However, growing evidence shows similar associations in individuals without these conditions. We therefore set out to systematically review the literature on this topic. MEDLINE searches were conducted of medical subject-headings *neuropsychology, cognition, cognition disorders, or neuropsychological tests*, cross-referenced with *oxidative stress, or superoxide*. Exclusion criteria were dementia and stroke studies, absence of human subjects, and absence of quantifiable oxidative stress/cognition measures. The search yielded 883 results, of which 19 studies (consisting of 3662 total subjects) were included in this review. The majority of studies indicated that frontal cognitive functions were most often impaired, and lipid peroxidation was most commonly associated with impairments. Literature on learning, memory, and general cognitive function was less robust. A substantial proportion of the literature on this topic is based on psychiatric populations. Frontal-executive dysfunction implicates frontal brain regions, which are known to be susceptible to oxidative damage. Further studies are needed, and those examining psychiatric populations may be especially fruitful. Focusing on youth may yield enhanced signal detection. Further study is needed to identify which antioxidant interventions work best for which cognitive functions and for which patients.

Contents

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1. Introduction

Oxidative stress is a process that involves the production of highly reactive oxidizing factors, such as free radicals and reactive oxygen species (ROS), and the inability of cellular antioxidant defenses to detoxify these compounds (Wallace, 1999). Protracted oxidative stress and exposure to radicals can cause damage to DNA, lipids, and proteins within the cell (Wallace, 1999). Most of these radicals are created in the mitochondria during the process of oxidative phosphorylation, and can diffuse into the cytosol and cause extra-mitochondrial damage (Figueira et al., 2013). Superoxide (O_2^-) is one of the most important initiating radicals in the process of oxidative stress generation, and results in the production of hydrogen peroxide through the enzyme superoxide dismutase (SOD) in addition to its own ability to cause oxidative damage (Sies and Cadenas, 1985). The process of lipid peroxidation occurs when unsaturated fatty acid chains are damaged by these radical molecules, and the resulting alkyl radicals react with hydrogen peroxide to form aldehydes such as the 4-hydroxyakenals (referred to as lipid peroxidation end-products) (Sies and Cadenas, 1985). These end products have powerful cytotoxic effects that can result in cellular and organ damage, in addition to disturbing the normal biological function of the molecule.

Human neurons contain high numbers of mitochondria, which makes the brain particularly susceptible to ROS and free radical production (Kapogiannis and Mattson, 2011). Furthermore, the brain is replete with unsaturated fats, which are particularly vulnerable to lipid peroxidation (Talarowska et al., 2012). These fats are found in both gray and white matter, the latter of which contains lipid-rich myelin which is critical for proper neuronal function (Durand et al., 2012). Taken together, this renders the brain an especially vulnerable organ to oxidative stress (Packer, 1992; Reisner, 2013). Endogenous antioxidant factors (e.g. glutathione (GSH) SOD, catalase) work to attenuate the effects of free radicals by enzymatically degrading or scavenging for free radicals to bind them and form less reactive complexes (Halliwell, 1996). These endogenously produced compounds are assisted by exogenous compounds (such as carotenoids and vitamin E) that are primarily derived from dietary sources (Sies and Stahl, 1995). The balance between oxidant and antioxidant factors determines overall oxidative stress, and the extent to which pro-oxidant factors can cause damage (Querfurth and LaFerla, 2010).

Oxidative stress has been implicated in neurodegenerative disease states such as mild cognitive impairment (MCI), and Alzheimer's disease (AD) (Albarracin et al., 2012; Kapogiannis and Mattson, 2011; Simonian and Coyle, 1996). Furthermore, cognitive dysfunction has been associated with oxidative stress in the aging process and these neurodegenerative conditions, which stands to reason given the vulnerability of the brain to oxidative damage (Kapogiannis and Mattson, 2011). A review of populations with MCI and dementia found repeated evidence of associations between oxidative stress and cognition (Cunningham et al., 2014; Mulero et al., 2011). In these clinical neurological conditions there are structural changes that occur in the brain which may give rise to cognitive deficits (Querfurth and LaFerla, 2010). However the association between oxidative stress and cognitive function is not limited to neurodegenerative diseases, MCI and AD. Oxidative stress has been implicated in a number of psychiatric disorders, and has been associated with the degree of psychopathology as well (Bourne et al., 2013; Flatow et al., 2013; Palta et al., 2014; Zhang et al., 2013b).

Despite accumulating studies evaluating oxidative stress and cognition among patients without dementia or stroke in recent years (particularly in the past five years), there has not been, to our knowledge, a published systematic review of this topic. The aim of this review is to examine the current literature on oxidative stress and cognition in individuals without stroke, neurodegeneration, MCI, and/or AD. Focusing on other psychiatric populations may offer insights regarding populations in which the therapeutic benefits of ameliorating oxidative stress may be optimized. Therefore, the manuscript concludes with suggestions regarding potential future therapeutic directions.

2. Methods

A systematic review of the literature on oxidative stress and cognitive function was performed using The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see Fig. 1) (Knobloch et al., 2011). MEDLINE searches were conducted with all articles published from 1946 to November, Week 3, 2014 using the following keywords and medical subject heading terms: *neuropsychology, cognition, cognition disorders, or neuropsychological tests,* each cross-referenced with *oxidative stress, or superoxide.* The resulting search was then restricted to human studies only. Search results were screened by reading study titles and abstracts in a consistent manner using inclusion and exclusion criteria described below. The full text of those articles meeting these criteria were read in greater detail. Studies in the reference lists of articles included in this review were screened by title only to determine their eligibility.

Studies in English, with quantitative measures of either oxidative stress markers or antioxidant compounds, and quantifiable scores on cognitive tests were included. Studies not in humans, or those involving subjects with stroke, dementia, MCI and/or other neurodegenerative diseases were excluded from the literature review (unless data for these subjects and non-affected subjects were reported separately). Studies were not excluded on the basis of sample size, but review articles were excluded unless previously unpublished data were presented.

3. Results

3.1. Study selection and exclusion

The literature search yielded a total of 883 studies. Upon removing duplicates ($n=95$), 788 studies remained that were screened. Of these studies, 769 were excluded (population with dementia=250, population with MCI=52, post-stroke population=11, no quantitative measure of cognition or oxidative stress=238, not in humans=141, review articles that did not report new data=66, not in English=11). Nineteen studies were selected for final inclusion. No additional studies were found upon examination of the reference lists of these

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