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Dementia – Unifying Mechanism Involving Antioxidant Therapy: Reactive Oxygen Species, Oxidative Stress, and Phenolics.

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Abstract

Reactive oxygen species (ROS) and oxidative stress (OS) play roles in dementia, as also in Alzheimer's (AD), Parkinson's (PD) disease and Schizophrenia (SCZ). Various sources, including oxidases, serve as generators of ROS-OS, such as mitochondria, NADPH, cytochromes P450, monoamines, ET metal complexes, G72 gene, and microglia. Diverse types of antioxidants (AOs) exert a positive influence on the harmful effects. A unifying mechanism based on ET-ROS-OS-AO is involved. Drugs for treatment of dementia are discussed in relation to the unifying theme.

Keywords: *Dementia; Radicals; Oxidative stress; Reactive oxygen species; Antioxidants*

Abbreviations: ET: Electron transfer; ROS: Reactive oxygen species; OS: Oxidative stress; AO: Antioxidant; SCZ: Schizophrenia; AD: Alzheimer's disease; PD: Parkinson's disease

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Introduction

Symptoms

Dementia is a term of medieval origin from the Latin *demens* meaning out of one's mind [1]. Contemporary usage of the term is a syndrome of progressive and persistent decline in multiple cognitive domains with associated changes in behavior, personality, and/or social functioning, produced by brain impairment. Senile dementia is the most common cause of dementia syndrome in a rapidly aging world. Memory impairment is the key cognitive domain, followed by frontal executive, language, and spatial dysfunctions. The most common dementia type associated with aging remains Alzheimer's disease, followed by dementia with Lewy bodies and vascular dementia. Clinical features suggesting dementia with Lewy bodies include hallucinations, deficits in attention with fluctuations in cognition, mild Parkinsonism with progressive gait disorder and falls, and early visuospatial deficits; memory complaint or impairment is common, but less severe. Clinical features are mild memory impairment and mild behavioral changes. The diagnosis of vascular dementia is assisted by the presence of vascular risk factors and clinical and/or imaging evidence of strokes. Senile dementia is often a mix of these common

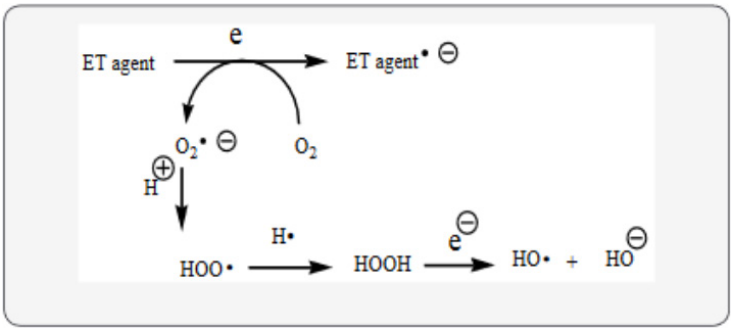
dementia types. The dementia syndrome may also be caused by external insults (such as vasculitis, toxins, drugs, infectious agents, brain trauma, systemic organ failure) and caused by other systemic disorders, including disturbance in thyroid, vitamin, and calcium metabolism, although rarely.

Symptoms of dementia emerge slowly and get worse over time [2]. There may be difficulty with complex mental tasks as well as with mood and behavior. There are problems with speaking and personal care, as well as hallucinations and delusions. They may not recognize their surroundings or other people and there is difficulty with language and performing acts. Dementia is a pattern of mental decline caused by different diseases or conditions, such as when brain cells (neurons) die, and connections between neurons are interrupted, which usually cannot be reversed. Alzheimer's disease causes over 60% of all dementia. Vascular disease, such as stroke, is the second most common cause. In the developed nations, about 15% of people older than 65 are thought to have dementia.

The strongest risk factor for dementia is age [1]. Other neurodegenerative diseases progress to age-related dementia including dementia with Lewy bodies and Parkinson disease dementia; less common frontotemporal dementias are cortico-basal degeneration and progressive supranuclear palsy, motor neuron disease, and other rarer types of dementia. Mid-life vascular factors, causing later-life small vessel vascular brain disease, have also come to be regarded more as risk factors for mixed pathology senile dementia than as common predictors of vascular dementia. Much of the recent focus has been on memory-defined mild cognitive impairment, predicting progression to Alzheimer's disease.

Unifying Mechanism

Dementia fits into the unifying mechanism which has been widely applied, previously in an article involving electron transfer (ET), reactive oxygen species (ROS) and oxidative stress (OS) [3]. This unifying mechanism argues that the preponderance of bioactive substances, usually as the metabolites, incorporate ET functionalities. We believe these ET-metabolites play an important role in physiological responses. The main group includes quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derviatives), and conjugated imines (or iminimum species). Resultant redox cycling is illustrated in Scheme 1. In vivo redox cycling with oxygen can occur, giving rise to OS through generation of ROS, such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide) (Scheme 1). Cellular and mitochrondrial enzymes can also perform catayticallly in the reduction of O_2.



Scheme 1: *Redox cycling with superoxide and ROS formation.*

In some cases, ET results in involvement with normal electrical effects (e.g. neurochemistry). Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range. Hence, ET in vivo can occur resulting in production of ROS, which can be beneficial in cell signaling at low concentrations, but produce toxic results at high levels. Electron donors consist of phenols, N-heterocycles or disulfides in proteins, which produce relatively stable radical cations. ET, ROS and OS have been increasingly implicated in the mode of action of drugs and toxins, e.g. anticancer drugs [4], carcinogens [5], cardiovascular toxins [6], toxins [7], ototoxins [8] and various other catagories [9].

In addition to the above, there is a plethora of experimental evidence supporting the theoretical framework. This evidence includes generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, and DNA oxidation and cleavage products, as well as electrochemical data [10]. This comprehensive, unifying mechanism is consistent with the frequent observation that many ET substances display a variety of activities (e.g. multiple-drug properties), as well as toxic effects. It is important to recognize that mode of action in the biodomain is often involved with many physiological actions and is multifaceted. In addition to ET-ROS-OS in relation to mechanism, much attention in the literature is paid to AO action entailing physiological action.

ROS-OS

ROS can be beneficial, but at high levels toxic effects often predominate. There are various sources for these species [11]. NAPDH oxidase is an important producer of the ROS in various organs. The G72 gene increased radical generation in cells. The gene acts as an activator of oxidase. ROS generated by NO synthase have been implicated in an array of harmful behaviors. Mitochondia provide another source of ROS-OS which appears to contribute to aging. Leakage of electrons occurs in the ET chain which react with oxygen to produce superoxide, a precursor of other ROS. Other examples of ROS producers are cytochrome P450, metal complexes, monoamine oxidase and microglia.

Drugs Used in Dementia Treatment

The major associate of dementia is AD, both of which are neurodegenerative disorders [12]. AD is the common most reason for dementia in the elderly [13]. There are various other reports that link the two illnesses [14-24]. In addition to these articles, there are assorted others that associate dementia with the unifying theme of ROS-OS-AO [25-30]. The literature deals with various drugs that are used for treatment of dementia. OS is believed to be the main risk for dementia and several of these studies deal with oxidative and AO markers in dementia patients [27-31]. Higher levels of AO power counter increased OS. Phenolics or their derivatives play important roles due to their AO and neuroprotective potential in the prevention of dementia, as in the case of PD and AD. Another important reference is a recent review concerning novel structure-activity relationship and quantitative data for phenolic drugs involving Alzheimer's and Parkinson's disease [32], which is applicable to dementia, as in importance of the substituent para to phenolic hydroxyl. Another factor is the presence of more than one phenolic group in the drugs discussed.

Phenols and Phenolic derivatives

Caffeic acid phenethyl ester (CAPE) (Figure 1) is a natural polyphenolic substance attributed with AD immunomodulatory and neuroprotective properties [25]. The drug arrested development of cognitive defecits in rats with dementia. Glutathione (GSH) content was enhanced, accompanied by decreased measure in rat

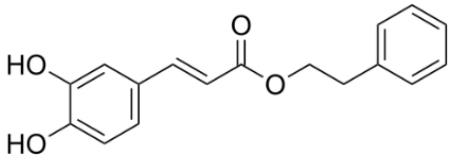


Figure 1: *Caffeic acid phenethyl ester (CAPE).*

Diarylpropionitrile (Figure 2), a diphenolic, is a synthetic, nonsteroidal, estrogen receptor ligand that protects neurons in dementia through various mechanisms, including anti-oxidation, anti-apoptosis and anti-inflammation [17].

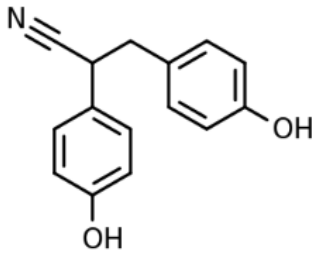


Figure 2: *Diarylpropionitrile.*

Puerarin (Figure 3) exerts various positive effects in vascular dementia, such as, decrease in malondialdehyde levels; GSH and total thiol levels were restored; apoptosis was reduced, and scavenging of ROS occurred [33]. Similar results were observed with Gastrodin (Figure 5) which is further discussed with the phenolic derivatives. [34], the polyphenol AO resveratrol (Figure 4) in nanoparticles attenuates mitochondrial OS in vascular dementia [35]. The agent improved redox rates and superoxide dismutase (SOD) activity.

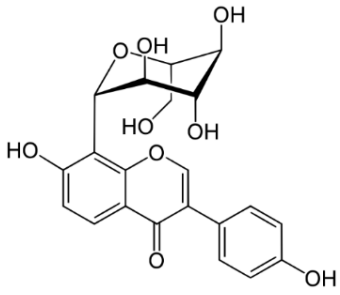


Figure 3: *Puerarin.*

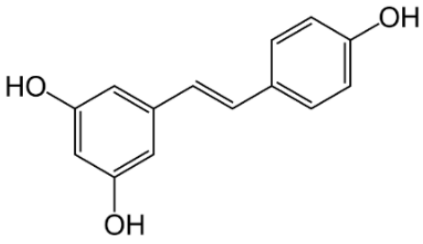


Figure 4: *Resveratrol.*

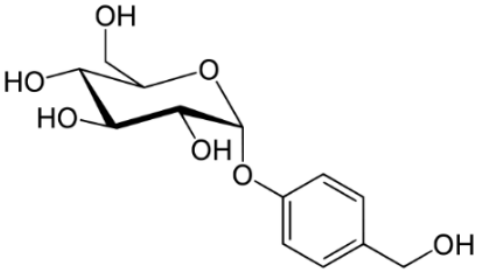


Figure 5: *Gastrodine.*

Gastrodine (Figure 5), a phenolic ether, exerts various positive effects in vascular dementia, decreasing MDA levels and restoring total thiol levels [34]. Scavenging of ROS occurred and a reduction of apoptosis. Aspirin (Figure 6), a phenolic ester that on hydrolysis yields the phenolic salicylic acid, was studied for its effect on OS and homocysteine [36]. Aspirin was effective in reducing factors associated with cognitive impairment in people at risk of dementia.

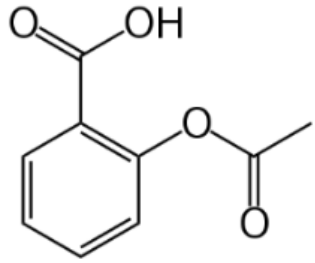


Figure 6: *Aspirin.*

Disulfide and Thiolsulfinate

A 2014 study reported beneficial effects of α-lipoic acid (Figure 7) complex on rats with dementia [36]. The supplementation of α-lipoic acid improved their AO status. Garlic, which contains sulfur AOs, such as allicin (Figure 8), has been studied extensively for health benefits [30]. In a number of studies, garlic preparations protect neuronal cells against β -amylod toxicity and apoptosis [32]. The broad range of AO and anti-apoptotic effects afforded by garlic also provides protection against dementia.

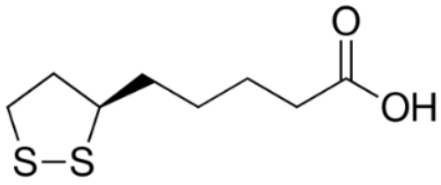


Figure 7: *α-lipoic acid.*

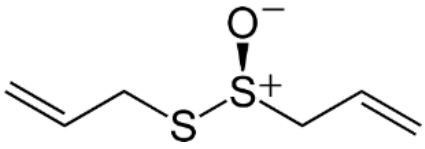


Figure 8: *Allicin.*

Other Drugs

Simvastatin (Figure 9) exerts benefits in the progression of senile dementia [37]. The drug regulates SOD, ROS, catalase and GSH in OS. Additionally, there is prevention of memory lapses. Hu-Yi-Neng, a diet supplement, including the AO ginko biloba, exerts a protective effect against OS [31]. Non-drugs such as acupuncture [38,39] and certain vitamins [40] are also reported to exert a positive effect on dementia.

Conclusion

Various drugs have proven effective in treatment of dementia. The major ones are phenolic, followed by sulfur containing ones, similar to AD and PD. Structure activity relationship (SAR) is applicable, as for AD and PD [41]. More work is needed on the important aspects of prevention and cure for the various brain illnesses.

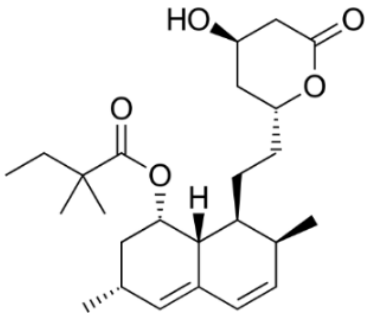


Figure 9: *Simvastatin.*

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