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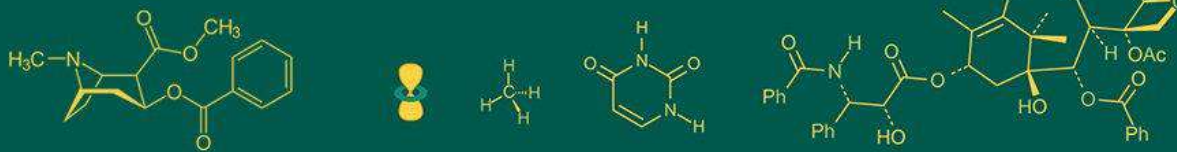
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Attention-deficit/hyperactivity disorder – unifying mechanism involving antioxidant therapy: Phenolics, reactive oxygen species, and oxidative stress

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Abstract
Reactive oxygen species (ROS) and oxidative stress (OS) play roles in Attention-Deficit/Hyperactivity Disorder (ADHD), as also in Alzheimer's disease (AD), Parkinson's disease (PD), Dementia, Schizophrenia (SCZ), Multiple Sclerosis (MS), Huntington's Disease (HD), and Depression. 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. Methylphenadate (MPH) is a widely favored drug for ADHD; however, there is considerable ROS-OS and AO action is less clear. Nevertheless, a proposal for the AO action is offered. MPH's dopaminergic action provides additional support for quinone formation, similar to dopamine. There are appreciable numbers of phenol and phenolic ether drugs, as for AD (1) and PD (2). A unifying mechanism based on ET-ROS-OS-AO is involved. Other possible influential aspects are discussed in a multifaceted approach.

Keywords: ADHD, radicals, oxidative stress, reactive oxygen species, antioxidants

Introduction
Attention-Deficit/Hyperactivity Disorder (ADHD) fits into the unifying mechanism, which has been widely applied previously as set forth 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 include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). Resultant redox cycling is illustrated in Scheme 1. *In vivo* redox cycling with oxygen can occur, giving rise to oxidative stress (OS) through generation of reactive oxygen species (ROS), such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide) (Scheme 1). Cellular and mitochondrial enzymes can also perform catalytically in the reduction of O_2.

Scheme 1: Redox cycling with superoxide and ROS formation.
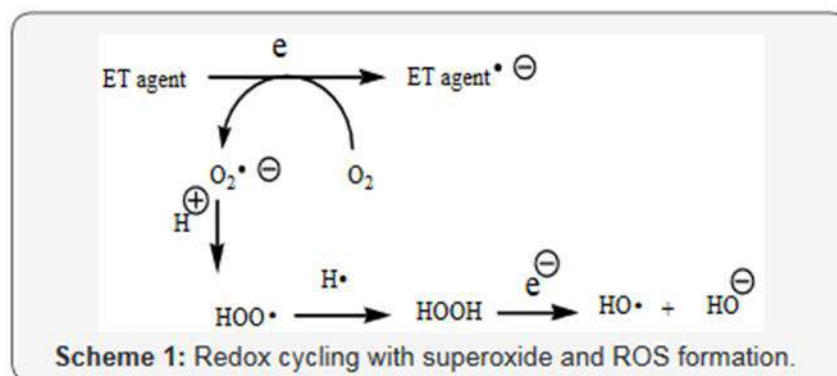
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In some cases, ET results in involvement with normal electrical effects (e.g. neurochemistry). Generally,

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 [4]. 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 [5], carcinogens [6], cardiovascular toxins [7], toxins [8], ototoxins [9] and various other categories [10].

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 [3]. 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.

Symptoms

The main characteristics of ADHD are inattention, hyperactivity, and impulsivity [11]. Detailed aspects are inattention with tasks, alertness, arousal and distractibility. Self-management, such as problems with self-instruction and anger control. Psycho stressors such as poverty, high parental stress, less affection, limited parental interaction, and family dysfunction can exacerbate these characteristics.

At the more basic, chemical level, research points to problems arising from dysfunction in frontal-striatal networks, as well as other brain regions, such as basal ganglia. There is evidence for genetic transmission of ADHD involving the dopamine systems that innervate frontal-striatal regions. ADHD is usually diagnosed in childhood and people with ADHD likely have an underlying genetic vulnerability to developing it [12]. There may be environmental factors that further complicate ADHD (eg. stressors such as family dysfunction); however, these factors are not causal. As noted, conflict and stress tend to make it worse. Diagnosis should be made carefully, since a high level of activity and occasional impulsiveness or inattentiveness is often normal in a child.

Hyperactivity and inattention compose the two major groups of characteristics of ADHD. Some of the more common aspects are carelessness, difficulty paying attention, trouble organizing, avoiding tasks that require sustained attention, misplacement or loss of items, easily distracted, and forgetfulness. More common characteristics of hyperactivity are excessive restlessness, inability to sustain quiet activities, driven behavior, excessive talking, impulsive behavior, difficulty waiting or impatience, and intrusive behavior like interrupting others. Often children with ADHD also display symptoms of other behavioral disorders such as learning disabilities. There is no single test to diagnose ADHD, so careful observation and evaluation by a specialist is necessary, since other conditions have similar symptoms of ADHD [12].

ROS-OS

It is necessary to recognize the importance of the multifaceted nature of physiological action. In addition to ET-ROS-OS-AO, other factors are at play in HD as indicated in this discussion: cell signaling, mitochondria, receptor binding and enzyme inhibition [13]. The literature addresses the basic aspects of these items: cell signaling [14], mitochondria [8], and receptor binding [15]. The related articles on PD and AD deal with the role of AOs in decreasing ROS-OS. However, the specific source of the harmful species was not addressed. Information is available on generation of ROS-OS in the brain.

ROS can be beneficial, but at high levels, toxic effects often predominate. There are various sources for these species [3]. 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. Mitochondria 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.

Discussion

Methylphenidate (MPH) (fig. 1) is a dopamine inhibitor used for treatment of ADHD [16]. Low doses of MPH decreased production of ROS and malondialdehyde (MDA). There was favorable AO increase in glutathione (GSH) and superoxide dismutase (SOD). Inhibition also occurred.
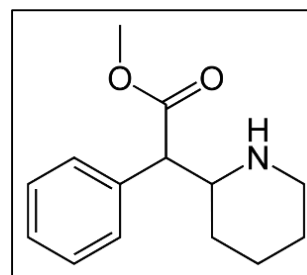

Fig 1: Methylphenidate (MPH)

Baicalin (fig. 2), a natural flavonoid, exhibits various properties, such as AO, antiapoptotic [16], and anti-inflammatory [17]. ADHD is closely related to dopaminic deficiency. The drug may protect dopaminergic neurons and increase dopamine.
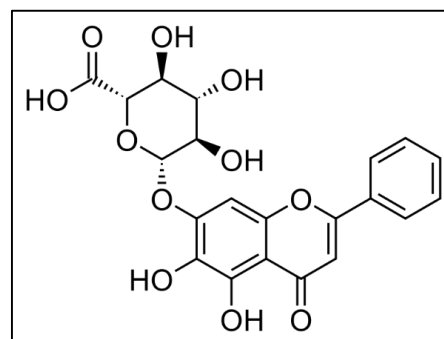

Fig 2: Baicalin

In ADHD patents, post treatment OS index values were significantly lower than the pre-treatment values [18]. Oxidative metabolism was impaired. MPH repaired the oxidative balance by increasing AO defense mechanisms.

Ginko biloba extract and pycnogenol (fig 3), a polyphenol and phenolic ether, could become supplements in ADHD

treatment [19]. Ginko Biloba extract contains phenolic acids, proanthocyanidins, flavonoid glycosides, such as myricetin, kaempferol, isorhamnetin and quercetin, and the terpene trilactones, ginkgolides and bilobalides. All of these are phenolic AOs with the exception of the last three which are weaker, less effective alchohol AOs.
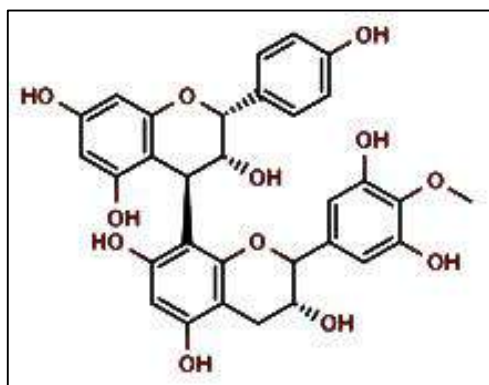

Fig 3: Pycnogenol

Polyphenolic compounds can be involved in treatment. Increased OS was inhibited by various polyphenols. These AOs in the diet have the potential to become medicants [20]. Growing evidence supports the use of N-acetylcysteine (fig 4), an AO thiol, in treating psychiatric and neurological disorders, which involve OS, mitochondrial dysfunctions, neuro inflammation, and apoptosis [21]. Preliminiary evidence supports favorable results with ADHD.
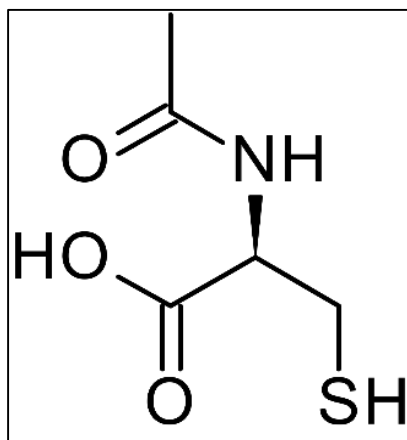

Fig 4: N-acetyl cysteine

The importance of catecholamines, like dopamine (figure 5), is supported by the effective treatment of ADHD [22]. Evidence for the therapeutic efficacy of AO-related therapies is discussed. Interventions involving AO mechanisms are addressed. There is interest in OS and nitrosative stress as contributors to the ADHD condition.
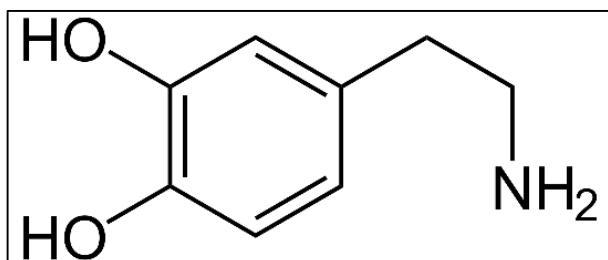

Fig 5: Dopamine

Many children with ADHD disorder have sleep disorders and can benefit from melatonin (fig 6) treatment [23]. The compound decreases sleep onset latency and increases total sleep time. Animal studies have confirmed a neuro protective effect, suggesting a role in minimizing neuronal damage. Melatonin is a phenolic ether which my cleave to the AO phenol (HG, p.193-194)
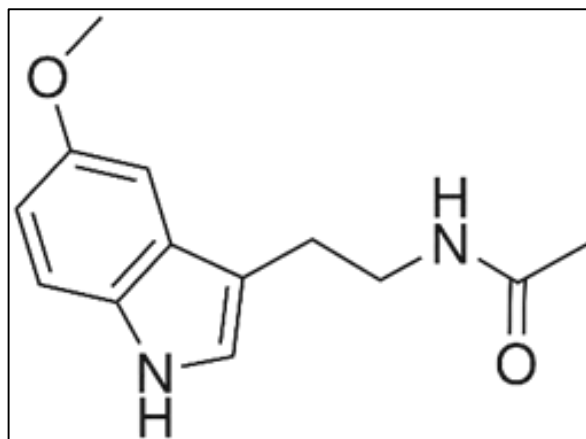

Fig 6: Melatonin

Dock proteins, mainly expressed in the CNS, play a role in protecting ganglion cells from neurotoxcity and OS [24]. The proteins are potential targets for various diseases, including ADHD. Their therapeutic potential is related to neuro protection and axon regeneration.

In MPH there is evidence for increased OS, altered AO defense and neuro inflammation in ADHD children [25]. Gumoricht and Rockway's 2014 study suggests that ω- 3 fatty acids and vitamin E (fig. 7) increased with tocotrienol (fig 8), a potential AO phenol, and reduced symptoms of neuro disorders, including ADHD.
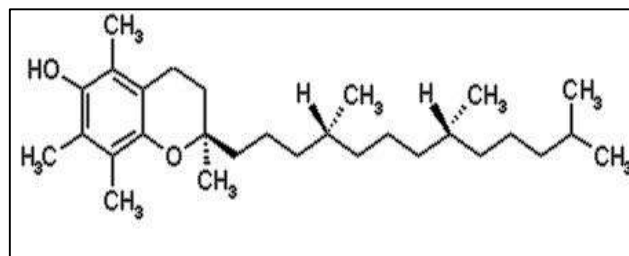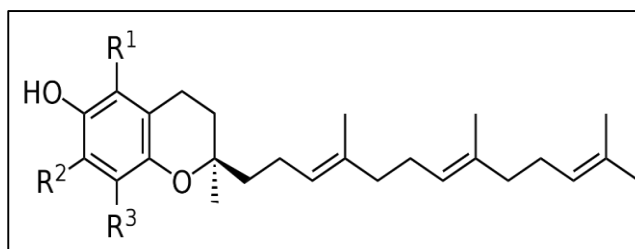

Fig 7: Vitamin E

Fig 8: Tocotrienol

YY162, consisting of Ginko biloba and ginsenoside Rg3 (fig. 9), an alcohol AO, attenuated increase in ROS, OS and ADHD behavior [26]. Interactive signaling between AO potential and the receptor is important for YY162 mediated neuro protective activity.
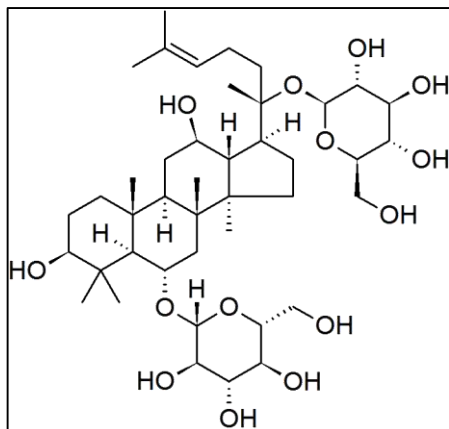
Fig 9: Ginsenoside

Decrease in ω- 3 fatty acids, like α-Linolenic acid (fig. 10), and an increase in OS or inflammation may contribute to brain disorders, such as ADHA (27). Dietary supplements of the acids decreased OS and inflammatory medications.
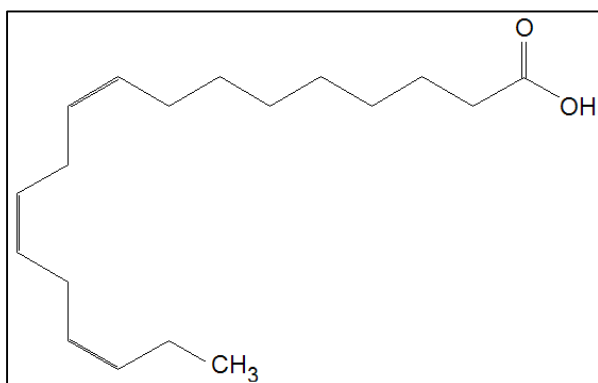

Fig 10: α-Linolenic acid

Evidence suggests that polychlorinated biphenyls (PCBs) may play a role in ADHD behavior (28). PCBs are known to generate OS via production of ROS. The model compound employed is 4-chlorobiphenyl. Oxidation produces 4-chlorobiphenyl – 2, 5 – hydroquinone, which undergoes further oxidation to the corresponding quinone (fig. 11). The introduction classifies quinones as a major type of ET agent which is capable of generating ROS-OS.
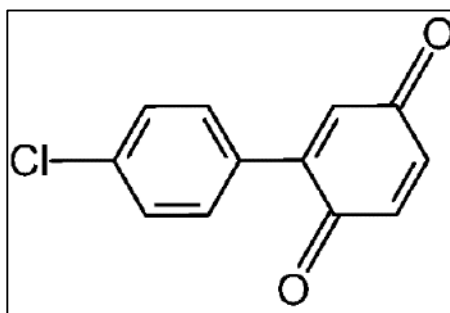

Fig 11: 4-chlorobiphenyl – 2, 5 – benzoquinone

OS has been implicated in the pathogeneses of diverse disease states (29). Evidence is accumulating for oxidative mechanisms in ADHD. The findings may introduce new targets for therapeutic interventions.

Insight regarding the AO action and ROS-OS from MPH is more elusive. One approach entails oxidation in the para position to a phenol with ensuing oxidation to the ET o –

quinone (Fig 12). Analogy can be found in oxidation of phenylalanine to tyrosine, followed by hydroxylation (30) and then presumably oxidation to the ET o – quinone. Protein modified tyrosine can be oxidized to the quinone methide [31]. Additionally, quinine methide is believed to play an important role in biosynthesis and in bioactivity of antitumor compounds [32]. The phenolic tyrosine and the diols may also serve as AOs.
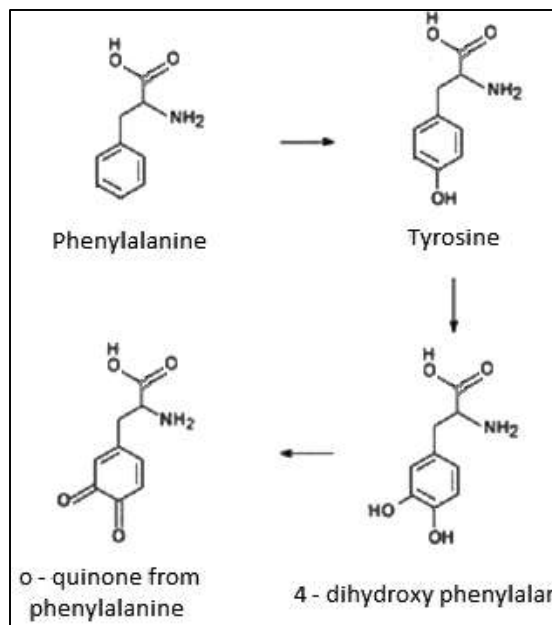

Fig 12: o-Quinone from Phenylalanine

Methylphenidate (MPH) is the drug of choice for treatment of ADHD (Nam). However, adverse side effects severely hamper its use. Conversion of MPH to phenols and subsequently to quinone, which produces ROS-OS, is not surprising since these entities are commonly involved in brain illnesses and their treatment. MPH action may be facilitated by making use of tyrosine enzymes which lead to both AO action and toxicity from ROS-OS.

Another possibility for ROS-OS toxicity by MPH involves metabolism to an N – nitrone derivative leading to ROS-OS. Support is provided by a report on OS induced by N – nitrosamines [33]. Lipid peroxidation increased rapidly with decrease in AO retinol. Increased ethane exhalation is a marker of OS. The unusual behavior of MPH may be a result of rapid enzyme catalyzed reactions leading to both AO and ROS-OS entities. In this regard, there is similarity to L-dopa and dopamine in PD [2].

In addition to the amino acid segment, there are two other portions of MPH that display physiological activity, namely phenethylamine and piperidine. A study was made of pharmacological characterization of piperdine ethers and dual activity norepinephrine inhibitors and serotonin agonists [34]. There is also a related report dealing with a piperdine derivative as histamine receptor ligands [35]. A review covers phenethylamine as a designer drug [36]. These drugs have increased in popularity. The "legal" drugs mimic the euphoric effects of well-known illicit drugs. There is similiarity in structure to MDMA (Ecstasy). Related compounds are analogs of mescaline [37]. Health complications and fatal overdose have put the spotlight on the phenethylamine types.

This drug is unusual in being favored for widespread use while at the same time producing many adverse side

eff4ects. This section addresses mechanistic aspects of both AO and ROS-OS. Use of MPH has increased in recent years according to a 2012 report [38]. Rates showed greater sensitivity to oxidative effects promoted by the drug. The study revealed increased lipid peroxidation and protein damage. MPH is a central stimulant prescribed for treatment of ADHD [39]. The drug can reduce OS, neuro-inflammation and neuro-degeneration. Treated rats exhibited decreased AO enzymes and increased lipid peroxidation was observed, which is an adverse toxic effect. Results demonstrated that MPH decreased TBARS and non-enzymatic radical – trapping AOs. There was increase in SOD and catalase (CAT) activities. The findings suggest alteration in AO defenses and oxidative adaptations.

Acute and chronic use of MPH was associated with increased OS and alterations in energy metabolism [40]. There was increase in TBARS and carbonyl groups, apparently from protein oxidation, and a decrease in SOD and CAT activities, presumably from undesirable oxidation. Psychostimulants, such as MPH, can cause long lasing neurochemical and behavioral adapations [41]. Chronic exposure to the drug induces oxidative damage. High doses increased harmful lipid peroxidation.

An additional study of AO enzyme activities were investigated in MPH treatement (Gomes). The AO enzymes evaluated were SOD and CAT. In the acute and chronic treatments, the activity increased or decreased depending upon the brain region involved. Probably, AO activity of the enzymes was not enough to prevent MPH-induced oxidative damage in specific regions of the brain.

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