Oxidative and nitrosative stress in ADHD: possible causes and the potential of antioxidant-targeted therapies

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Abstract

Attention deficit hyperactivity disorder (ADHD) has a complex etiology although theories associated with disturbances in dopaminergic and noradrenergic activity are most commonly cited. The importance of these catecholamines in ADHD is supported by its effective treatment utilising stimulant and non-stimulant medications that modify their activity. Recently there has been interest in oxidative and nitrosative stress (O&NS) in ADHD and its potential to contribute to this condition. In this article, research investigating O&NS in ADHD is reviewed and its impact on catecholaminergic activity and neurological structure is discussed. Lifestyle, environmental, psychological and nutritional influences on O&NS in people with ADHD are reviewed and evidence for the therapeutic efficacy of antioxidant-related therapies is assessed. A selection of interventions with antioxidant mechanisms are presented as potential options for the treatment of ADHD. However, further research is required to help elucidate the role of O&NS and antioxidants for the prevention and management of ADHD.

Attention deficit hyperactivity disorder (ADHD) is a common behavioural disorder affecting 5 to 7 percent of school-age children (Willcutt 2012) and 2 to 5 percent of adults (Fayyad et al. 2007; Simon et al. 2009). It has a complex etiology although theories associated with disturbances in dopaminergic and noradrenergic neurotransmission have been the most predominant. In people with ADHD, the prefrontal cerebral cortex, caudate, and cerebellum have emerged as the primary areas showing deficits (Durston 2003; Seidman et al. 2005). These areas are important for the regulation of attention, thoughts, emotions, and behaviour. The network of activity in these areas is believed to be maintained by the neurotransmitters dopamine and noradrenaline (Sharma and Couture 2014).

ADHD is most commonly treated with stimulant medications such as methylphenidate and amphetamines, non-stimulants such as atomoxetine, and alpha2-adrenergic agonists such as clonidine and guanfacine. Through their effects on dopamine and noradrenaline transporters, stimulants inhibit the reuptake of dopamine and noradrenaline, thereby increasing the extracellular levels of these neurotransmitters. These stimulants also inhibit monoamine oxidase, the enzyme that metabolises these catecholamines (Wilens et al. 2011). Atomoxetine works as a selective reuptake inhibitor of noradrenaline leading to its increased extracellular concentration (Garnock-Jones and Keating 2009).

While effective, these medications are associated with several adverse effects. These include loss of appetite, growth delay and sleep disturbances (Cortese et al. 2013). It is important to note that despite their widely accepted short-term efficacy, the long-term effectiveness of pharmacological treatments on social, educational and occupational functioning in people with ADHD continues to be debated (Huang and Tsai 2011; Langberg and Becker 2012; Nijmeijer et al. 2008). On a positive note, recent analyses using the Swedish national registrar suggests that long-term stimulant use in people with ADHD is associated with reduced rates of substance use, criminality, and serious traffic accidents (Chang et al. 2014a; Chang et al. 2014b; Lichtenstein et al. 2012).

Despite wide appreciation of catecholaminergic theories associated with ADHD, there has been increased research into other biological mechanisms associated with ADHD. For example, in psychiatry there has been interest in immune-inflammatory pathways and oxidative and nitrosative stress (O&NS). In particular, it has been confirmed through recent meta-analyses that depression is associated with increased O&NS (Howren et al. 2009; Palta et al. 2014). In a meta-analysis of twenty-three studies with 4980 participants, Palta et al. (2014) confirmed a Cohen's d effect size of 0.55 for the association between depression and oxidative stress; and a smaller but statistically significant effect for the association between depression and antioxidant status markers (Cohen's d = -0.24). Increased O&NS has also been found in bipolar disorder (Andreazza et al. 2008; Brown et al. 2014),

with the results of a recent meta-analysis confirming increased lipid peroxidation, DNA/RNA damage, and nitric oxide in people with bipolar disorder compared to healthy controls (Brown et al. 2014). Increases O&NS has also been found in people with anxiety disorders (Hassan et al. 2014) and schizophrenia (Emiliani et al. 2014).

The purpose of this article is to review O&NS in ADHD, potential causes for O&NS, and how O&NS may impact on the etiology of ADHD. Finally, antioxidant therapies for the treatment of ADHD are reviewed and the potential of various antioxidant therapeutic options are discussed.

What is oxidative and nitrosative stress?

Reactive oxygen (ROS) and reactive nitrogen species (RNS), such as superoxide, nitric oxide, peroxynitrite and hydrogen peroxide are unstable molecules that can react with other cells in the body. They are generated during normal cellular metabolism, mainly formed within the mitochondria. ROS and RNS can also be generated from ultraviolet light irradiation, environmental pollutants, and by neutrophils, eosinophils and macrophages during inflammation. Via their influence on proteins, fatty acids and DNA, ROS and RNS have numerous essential physiological roles involved in the regulation of cellular function (Rahman 2007).

Under normal conditions, ROS and RNS are regulated by a balancing system comprising antioxidants, antioxidant enzymes and proteins. Antioxidants remove ROS and RNS by scavenging radicals and decreasing their production. Examples of scavenger antioxidants are coenzyme Q_{10} (CoQ10), vitamin C and E, and glutathione. ROS may also be neutralised by different antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase. Some proteins including acute phase proteins such as albumin, transferrin, haptoglobin and ceruloplasmin also function as antioxidants by binding ROS and RNS (Maes et al. 2011).

A state of O&NS occurs when there is an imbalance between ROS/RNS and antioxidant defences. Antioxidant defences may be compromised due to lowered antioxidant concentrations in the body and/or lowered activity of antioxidant enzymes. O&NS can be detrimental to the body leading to structural and functional changes producing cellular injury. An excess of ROS and RNS can cause damage to fatty acids, proteins and DNA. O&NS also has the capacity to damage mitochondrial defence systems, further perpetuating O&NS. Some organs, such as the brain, are more vulnerable to the detrimental effects of O&NS because of its high level of oxygen utilisation, high lipid content, and lower antioxidant concentration (Ikonomidou and Kaindl 2011).

Evidence for oxidative/ nitrosative stress (O&NS) in ADHD

Although findings are inconsistent, in a recent meta-analysis it was confirmed that ADHD is associated with increased oxidative stress (Joseph et al. 2013). Children and adults with ADHD have, on the whole, increased O&NS biomarkers in blood, urine and saliva. For example, elevated levels of malondialdehyde (MDA), a marker of lipid peroxidation have been found in children (Ceylan et al. 2010) and adults (Bulut et al. 2013; Bulut et al. 2007) with ADHD. However, lowered concentrations of MDA have also been identified in people with ADHD (Oztop et al. 2012; Spahis et al. 2008). There has also been confirmation of increased nitrosative stress as demonstrated by an increased concentration of nitric oxide in children (Ceylan et al. 2010) and adults (Selek et al. 2008), and increased activity of nitric oxide synthase in children (Ceylan et al. 2012). A summary of findings examining O&NS biomarkers in people with ADHD is presented in Table 1.

<<Insert Table 1 near here>>

In the same meta-analysis by Joseph and colleagues (2013) it was concluded that there was no evidence of discrepancy in antioxidant activity between people with ADHD and healthy, matched controls. As demonstrated in Table 2, investigations into antioxidant activity are generally inconsistent in people with ADHD. On the whole, differences have been observed although the direction of change is inconsistent. The discrepant findings may be due processes associated with the onset of an antioxidant defence system. That is, increases in antioxidant activity may not necessarily reflect a premorbid increased concentration but an upregulation in activity to combat increased free radical activity.

<<Insert Table 2 near here>>

While the findings to date suggest increased O&NS in people with ADHD, they are tempered by continued inconsistences. Biomarker measurement in psychiatry is still in its infancy, particularly relating to peripheral markers associated with O&NS. As observed in Tables 1 and 2 several markers have been measured, but no uniform 'ideal' biomarker or collection of biomarkers has been agreed upon. Currently MDA and markers associated with nitric oxide have received the most attention and most consistent findings. Antioxidant biomarkers such as paraoxonase-1 (PON-1) and superoxide dismutase also show promise as potentially reliable markers.

Collection, storage and measurement procedures also vary significantly across studies and there is still no agreement on 'gold standard' and user friendly collection and measurement protocols. In addition, further investigation is required to determine the extent of O&NS across gender and age. It is also plausible that O&NS is associated with certain ADHD subtypes and/or symptoms but this has not yet been adequately explored due to a lack of adequately powered studies.

Potential causes of O&NS in ADHD

While there is evidence of increased O&NS in ADHD, correlation does not confirm causation. O&NS can theoretically affect several biological pathways associated with ADHD, although it is equally plausible that other lifestyle, environmental, psychological and genetic factors associated with ADHD account for the observed increases. That is, greater O&NS may simply be an artefact associated with these various factors and have little to do with the actual etiology of ADHD. Alternatively, O&NS may play an important role in disturbing biological mechanisms associated with ADHD. Lifestyle, environmental, psychological and nutritional factors that may contribute to the increased O&NS observed in ADHD are reviewed below.

Diet quality is often believed to influence ADHD symptoms. Food colourings, additives, and unhealthy food choices are commonly reported to contribute to ADHD symptomatology, leading researchers to investigate the treatment efficacy of restriction and elimination diets (Heilskov Rytter et al. 2014; Nigg and Holton 2014). In prospective studies, consuming a Western dietary pattern or a high junk food diet during early childhood was associated with an increased risk of ADHD in later childhood and adolescence (Howard et al. 2011; Wiles et al. 2009). If diet has a role in the establishment of ADHD, prevalence rates should therefore vary across geographic regions with differing dietary patterns. However, no adequately controlled study has been identified investigating this area.

O&NS can be influenced by dietary patterns, with consistent findings of increased O&NS associated with Western dietary patterns and lowered O&NS associated with Mediterranean and traditional diets (Berk et al. 2013b; Lopresti et al. 2013). The consumption of synthetic food colourings and additives are also likely to impact on O&NS activity (Amin et al. 2010; El-Wahab and Moram 2013). In an animal study, the administration of several synthetic food colorants and flavour additives lowered blood and liver concentrations of reduced glutathione, glutathione-S-transferase and superoxide dismutase (El-Wahab and Moram 2013). Tartrazine administration for 60 days to male rats reduced testicular concentrations of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase (Visweswaran and Krishnamoorthy 2012). These synthetic colorants can alter concentrations of zinc, iron, copper and manganese which are all

essential cofactors for antioxidant enzymes (Cemek et al. 2014; Visweswaran and Krishnamoorthy 2012). Food colourings are also associated with increased immune reactivity which may be another mechanism associated with O&NS (Vojdani and Vojdani 2015).

Sleep disturbances are common in children with ADHD. This is characterised by sleep onset difficulties, sleep-disordered breathing, and frequent night-time awakenings (Hvolby 2014; Sedky et al. 2014). While there continues to be uncertainty about the direction of this ADHD-sleep relationship, it has been confirmed that sleep problems are associated with increased O&NS (Boudjeltia et al. 2011; Gulec et al. 2012), thereby presenting an additional contributory cause for the increased O&NS observed in ADHD.

Exercise influences antioxidant activity and consequent O&NS (Cooper et al. 2002; Radak et al. 2008). Although research is limited, television watching and computer usage is increased, and participation in sports is decreased in children with ADHD (Bener and Kamal 2014; Lingineni et al. 2012). Early television watching is also associated with attentional problems in later childhood (Cheng et al. 2010; Christakis et al. 2004), although this finding is inconsistent as null associations have also been found in several studies (Ferguson 2011; Stevens and Mulsow 2006)

ADHD is regularly associated with deficiencies in several nutrients influencing immune-inflammatory pathways and O&NS. Omega-3 essential fatty acids (EFAs) have effective anti-inflammatory and antioxidant effects and are consistently lowered in people with ADHD (Hawkey and Nigg 2014). Zinc has numerous biological roles in the body and has strong antioxidant activity (Prasad 2014). Zinc deficiency and reduced zinc concentrations are often found in people with ADHD (Arnold and DiSilvestro 2005), and this has been confirmed in a meta-analysis by Scassellati and colleagues (2012). More recently, lowered vitamin D levels and vitamin D deficiency have also been reported in people with ADHD (Bener and Kamal 2014; Goksugur et al. 2014). Vitamin D has significant immune-modulating effects (Gunville et al. 2013) and supplementation is associated with a reduction in oxidative stress (Shab-Bidar et al. 2014).

ADHD is also associated with an increased exposure to prenatal smoking (Keyes et al. 2014; Zhu et al. 2014), and post-natal exposure to lead and other environmental pollutants (Polanska et al. 2013; Yolton et al. 2014). Nicotine (Vargas et al. 2013) and lead exposure (Patra et al. 2011) can significantly increase free radical activity and subsequent O&NS.

Psychiatric disorders such as depression, anxiety conditions and bipolar disorder are all associated with increased O&NS (Andreazza et al. 2008; Hassan et al. 2014; Palta et al. 2014). As these disorders have an increased comorbidity with ADHD (Babcock and Ornstein 2009; Mao and Findling 2014), this could at least partly account for the increased O&NS observed in ADHD. In addition, several medical disorders, particularly atopic eczema and asthma, have an increased

prevalence in people with ADHD (Buske-Kirschbaum et al. 2013; Schmitt et al. 2010), with early childhood eczema a risk factor for the development of ADHD (Chen et al. 2014). Eczema is associated with increased oxidative stress and inflammatory response (Sivaranjani et al. 2013). There is also preliminary research to suggest that coeliac disease is over-represented in people with ADHD (Niederhofer 2011; Niederhofer and Pittschieler 2006), although negative findings have also been reported (Gungor et al. 2013). However, these medical and psychiatric disease cannot solely account for the increased O&NS in ADHD as in several studies these comorbidities were adequately controlled for in analyses.

Although in most of the cross-sectional studies cited above medication use was accounted for in statistical analyses, it is interesting to note that ADHD medications such as methylphenidate and atomoxetine have been shown in animal studies to influence antioxidant activity and O&NS. Findings are inconsistent with reports of positive (Schmidt et al. 2010; Schmitz et al. 2012a), adverse (Comim et al. 2014; Martins et al. 2006; Schmitz et al. 2012b) and null effects (Cöngöloğlu et al. 2006; Gomes et al. 2008). This makes conclusions about the impact of such medications on O&NS difficult as results seem to be influenced by treatment duration (acute versus chronic), age of population (young versus adult), brain region examined, biomarker measured, and dosage of drug administered. Further investigation in this area is required as it has potential treatment implications particularly relating to the role of adjuvant antioxidant-targeted treatments.

How O&NS and inflammation might influence biological pathways associated with ADHD

Structural deficits in the prefrontal cerebral cortex, caudate, and cerebellum are commonly observed in ADHD (Durston 2003; Seidman et al. 2005). Lower concentrations of neurotrophins such as brain-derived neurotrophin factor (BDNF) have also been identified in people with ADHD (Liu et al. 2014). BDNF has a critical role in hippocampal functioning, long-term potentiation for learning and memory, synaptic plasticity, neurogenesis, and neuroprotection (Leal et al. 2014). Damage to relevant brain structures and reduced concentrations of neurotrophin may at least be partly due to O&NS. The brain is particularly susceptible to O&NS because of its high oxygen utilisation and relatively low antioxidant concentration. The brain also has a high lipid concentration which is susceptible to damage from O&NS (Ikonomidou and Kaindl 2011). O&NS also seems to have detrimental effects on levels of BDNF (Jain et al. 2013; Zhang et al. 2014). Why damage resulting from O&NS occurs in selective brain regions associated with ADHD symptoms is yet to be determined but may be related to pre-existing genetic susceptibilities making these areas

vulnerable to O&NS damage. The timing of O&NS during critical maturation periods associated with these structural brain regions may also be a factor and requires investigation.

Dopamine, the primary neurotransmitter implicated in ADHD, is also influenced by O&NS. Elevated hydrogen peroxide suppresses striatal dopamine release (Avshalumov et al. 2005), and excess O&NS is involved in the degeneration of dopaminergic neurons (Tsang and Chung 2009). O&NS also influences dopamine receptor function (Sankhwar et al. 2013; Zeng et al. 2009). Nitric oxide also has an inhibitory effect on dopamine transporters and decreases hippocampal levels of dopamine (Kiss et al. 2004; Wegener et al. 2000).

5,6,7,8- tetrahydrobiopterin (BH4) is a rate-limiting enzyme associated with the biosynthesis of serotonin and the catecholamines dopamine, adrenaline, and noradrenaline. Increased output of ROS in macrophages over an extended period can destroy BH4, leading to a reduced capacity for dopamine and other neurotransmitter synthesis (Sperner-Unterweger et al. 2014). Reduced BH4 activity may therefore be another factor accounting for the dopaminergic and noradrenergic disturbances observed in people with ADHD.

It is important to note that the relationship between dopamine, noradrenaline and O&NS is bi-directional. While O&NS can influence levels of these neurotransmitters, these neurotransmitters have antioxidative and free radical scavenging properties (Yen and Hsieh 1997). Dopamine can also be easily oxidised into the metabolite dopamine quinone, which is highly reactive and can contribute to oxidative stress (Meiser et al. 2013; Miyazaki and Asanuma 2008).

The potential for antioxidant-related therapies in ADHD

Nutraceuticals and diet are the most well-recognised antioxidant therapeutic options. However, as noted in previous sections, O&NS can be caused by a large array of factors. Consequently, therapies that target these causes can also be classified as antioxidant therapies. For example, improvements in sleep, increased physical activity, and treatment of comorbid medical and psychiatric disorders may have antioxidant effects. These approaches should therefore be considered, particularly if they are found to have significance in an individual with ADHD. In fact, in several studies it has been confirmed that exercise (Wigal et al. 2013) and sleep interventions (Hvolby 2014) have the potential to improve a number of symptoms associated with ADHD. Whether changes in O&NS are necessary for symptomatic improvement is unknown at this time, as biomarkers are rarely examined during these interventions.

More 'traditional' antioxidant therapies are derived from dietary, nutraceutical or pharmacological options. In several studies dietary interventions comprising elimination and restrictive diets have shown promise as effective treatments for ADHD (Nigg and Holton 2014;

Stevenson et al. 2014). Although it requires significant effort and is difficult to maintain long-term, positive effects have been found following the implementation of very restrictive diets, such as the "few foods" diet (Pelsser et al. 2009). However, further research is required as the benefits of such interventions have been inconsistently confirmed in published meta-analyses. For example, a meta-analysis on artificial food colour exclusion revealed statistically significant moderate effects on ADHD symptoms, but when studies were restricted to trials on populations with no or low medication intake findings became non-significant. A meta-analysis by the same research group on elimination diets for ADHD revealed an overall significant large effect size, but this again became non-significant when only studies using 'probably-blinded assessments' were analysed (Sonuga-Barke et al. 2013). Stevenson and colleagues (2014) concluded that restricted elimination diets and artificial food colour elimination are potentially valuable treatments, but larger-scale, robust studies are required. Also requiring investigation are the mechanisms associated with such interventions. Beneficial effects on O&NS and inflammatory processes are likely as the consumption of a Western diet, and synthetic food colourings and additives are associated with increased O&NS (El-Wahab and Moram 2013; Lopresti et al. 2013).

Although research is still preliminary, there is evidence that agents with antioxidant activity are effective treatments for ADHD. *Pinus marinus* (French maritime pine bark) has strong antioxidant activity and has support for the treatment of ADHD. In a randomised, double-blind placebo controlled study, *Pinus marinus* was more effective than a placebo in reducing hyperactivity, and improving attention and visual-motor coordination in children with ADHD (Dvořáková et al. 2007; Trebaticka et al. 2006). In another study on adults with ADHD, *Pinus marinus* was as effective as methylphenidate, although neither was more effective than the placebo (Tenenbaum et al. 2002). These lack of significant findings from the two active treatment conditions may be due to the short treatment period of 3 weeks. The crossover design used in this study, comprising a short washout period of 1 week may have also impacted on the findings, as there were significant positive effects from all treatment conditions.

Zinc has strong antioxidant properties and also has support as a stand-alone treatment in reducing hyperactivity and impulsivity, but not inattention in children and adolescents with ADHD (Bilici et al. 2004). As an adjunct treatment to methylphenidate, zinc also enhanced treatment gains compared to methylphenidate and a placebo in children with ADHD (Akhondzadeh et al. 2004). However, in another randomised, double-blind, placebo-controlled study, zinc as a stand-alone or adjunctive treatment to methylphenidate was ineffective for treating ADHD symptoms (Arnold et al. 2011).

N-acetylcysteine (NAC), a precursor to the antioxidant glutathione, was effective for the treatment of ADHD symptoms in adults with systemic lupus erythematosus (Garcia et al. 2013). Interest in NAC has increased recently following promising findings for the treatment of several psychiatric disorders such bipolar disorder, depression and schizophrenia (Berk et al. 2013a). When used in conjunction with flax seed, vitamin C was also effective for the treatment of ADHD symptoms in an open-label study (Joshi et al. 2006).

In a meta-analysis by Block *et al.* (2011), omega-3 EFA supplementation, particularly formulations with higher doses of eicosapentaenoic acid, were confirmed to be modestly effective for the treatment of ADHD. The anti-inflammatory effects of fish oil are well recognised and in some clinical trials supplementation has been associated with reduced oxidative stress (Hariri et al. 2012; Mori et al. 2003).

While there is some support on the efficacy of the above-mentioned nutraceuticals, further high-quality studies on well-defined ADHD populations, using large sample sizes are required to help clarify their short and long-term efficacy. Other potential antioxidants included vitamin C, vitamin E and CoQ10. In addition, other nutraceuticals with significant antioxidant activity that merit investigation in ADHD treatment trials include curcumin, green tea and resveratrol. The psychotropic effects of curcumin, in particular, are intriguing, and there has been some support for it efficacy in the treatment of depression (Lopresti et al. 2014). Because of demonstrated vitamin D deficiencies in people with ADHD, supplementation with this vitamin and/or replenishment via sunlight exposure is an additional area requiring investigation. In fact, it has been found that living in regions with high solar intensity is independently associated with a lower prevalence of ADHD (Arns et al. 2013). As a result of its potential immune-regulating effects, there has also been interest in probiotic supplementation for depression and anxiety (Dinan et al. 2013) and it presents as another option for future study.

Conclusion and directions for future research

<<Insert Figure 1 near here>>

From research conducted so far, it seems that that ADHD is associated with increased O&NS. However, there continues to be inconsistency in findings and this may at least be partly attributed to differences in O&NS markers tested, samples used, populations examined, and testing and collection protocols utilised to examine relevant markers. Further investigation is therefore required

to help clarify the relevance of O&NS in ADHD and its applicability for the prevention and treatment of ADHD.

What remains uncertain is the importance of O&NS in ADHD. As reviewed in this article and summarised in Figure 1, several lifestyle, environmental, nutritional, psychological and medical factors can influence O&NS, and it remains to be determined whether increased O&NS is simply a mere consequence associated with these factors, or whether it contributes to the development or exacerbation of ADHD symptoms. Positive findings from treatment studies utilising antioxidant therapies suggest that O&NS may have some relevance in ADHD, although studies are small and require further validation through high-quality study designs, with large samples sizes. Examination of biomarker changes during intervention trials and their relationship to symptomatic change will also help clarify the relevance of O&NS in ADHD.

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Table 1. Summary of oxidative stress biomarkers examined in people with ADHD						
Reference	Sample size	Mean age	% male[1]	Psychotropic medication	Oxidative stress biomarker measured	Difference compared to controls
Ceylan et al. (2012)	35 (A) 35 (C)	10	69	No	Xanthine oxidase	↑ (serum)
Ceylan et al. (2012)	35 (A) 35 (C)	10	69	No	Adenosine deaminase	↑ (serum)
Oztop et al. (2012) Spahis, et al. (2008) Ceylan et al. (2010) Bulut, et al. (2013) Bulut et al. (2007)	30 (A) 30 (C) 37 (A) 35 (C) 35 (A) 35 (C) 35 (A) 29 (C) 20 (A) 21 (C)	9 9 10 25 28	75 73 69 71 70	No No No Yes Yes	Malondialdehyde	↓ (plasma) ↓ (plasma) ↑ (plasma) ↑ (plasma) ↑ (plasma)
Oztop et al. (2012)	30 (A) 30 (C)	9	75	No	Advanced oxidation protein products	= (plasma)
Archana et al. (2012)	20 (A) 20 (C)	9	70	No	Pseudocholinesterase	↑ (saliva)
Ceylan et al. (2010) Varol Tas et al. (2006) Selek et al. (2008)	35 (A) 35 (C) 30 (A) 51 (C) 20 (A) 21 (C)	10 9 28	69 100 70	No Yes No	Nitric oxide	↑ (plasma) ↓ (serum) ↑ (plasma)
Ceylan et al. (2012)	35 (A) 35 (C)	10	69	No	Nitric oxide synthase	↑ (serum)
Oztop et al. (2012)	30 (A) 30 (C)	9	75	No	8-Oxo-2'-deoxyguanosine	↓ (plasma)
Chovanova et al. (2006)	61 (A) 56 (C)	12	82	No	8-Oxoguanine	↑ (plasma)
Selek et al. (2012) Karababa et al. (2014)	50 (A) 31 (C) 32 (A) 32 (C)	25 31	70 68	No No	Total oxidative status	↑ (plasma) = (plasma)
Selek et al. (2012) Karababa et al. (2014)	50 (A) 31 (C) 32 (A) 32 (C)	25 31	70 68	No No	Oxidative stress index	↑ (plasma) = (plasma)

(A) = ADHD; (C) = control; [1]ADHD group only

Table 2. Summary of antioxidants biomarkers examined in people with ADHD						
Reference	Sample size	Mean age	% male[1]	Psychotropic medication	Antioxidant biomarker measured	Difference compared to controls
Çelik et al. (2013) Ceylan et al. (2010) Ruchi et al. (2011)	40 (A) 35 (C) 35 (A) 35 (A) 32 (A) 35 (C)	10 10 9	63 69 88	No No No	Catalase	= (plasma) ↑ (plasma) ↓ (saliva)
Çelik et al. (2013) Ceylan et al. (2012)	40 (A) 35 (C) 35 (A) 35 (C)	10 10	63 69	No No	Glutathione S-transferase	↑ (plasma) ↓ (serum)
Ceylan et al. (2010)	35 (A) 35 (C)	10	69	No	Glutathione peroxidase	↓ (plasma)
Ceylan et al. (2010) Russo (2010) Selek et al. (2008)	35 (A) 35 (C) 22 (A) 20 (C) 20 (A) 21 (C)	10 10 28	69 77 70	No No No	Superoxide dismutase	= (plasma) ↓ (serum) ↓ (plasma)
Çelik et al. (2013) Ruchi et al. (2011)	40 (A) 35 (C) 32 (A) 35 (C)	10 9	63 88	No No	Antioxidant activity	↑ (plasma) ↓ (saliva)
Selek et al. (2012) Karababa et al. (2014)	50 (A) 31 (C) 32 (A) 32 (C)	25 31	70 68	No No	Total antioxidative status	↑ (plasma) = (plasma)
Archana et al. (2012)	20 (A) 20 (C)	9	70	No	Ceruloplasmin	= (saliva)
Bulut et al. (2013)	35 (A) 29 (C)	25	71	Yes	Arylesterase	↓ (plasma)
Ceylan et al. (2012) Oztop et al. (2012) Bulut et al. (2013)	35 (A) 35 (C) 30 (A) 30 (C) 35 (A) 29 (C)	10 9 25	69 75 71	No No Yes	Paraoxonase-1	↓ (serum) = (plasma) ↓ (plasma)
Oztop et al. (2012) Archana et al. (2012)	30 (A) 30 (C) 20 (A) 20 (C)	9 9	75 70	No No	Thiol	= (plasma) ↑ (saliva)

(A) = ADHD; (C) = control; [1]ADHD group only

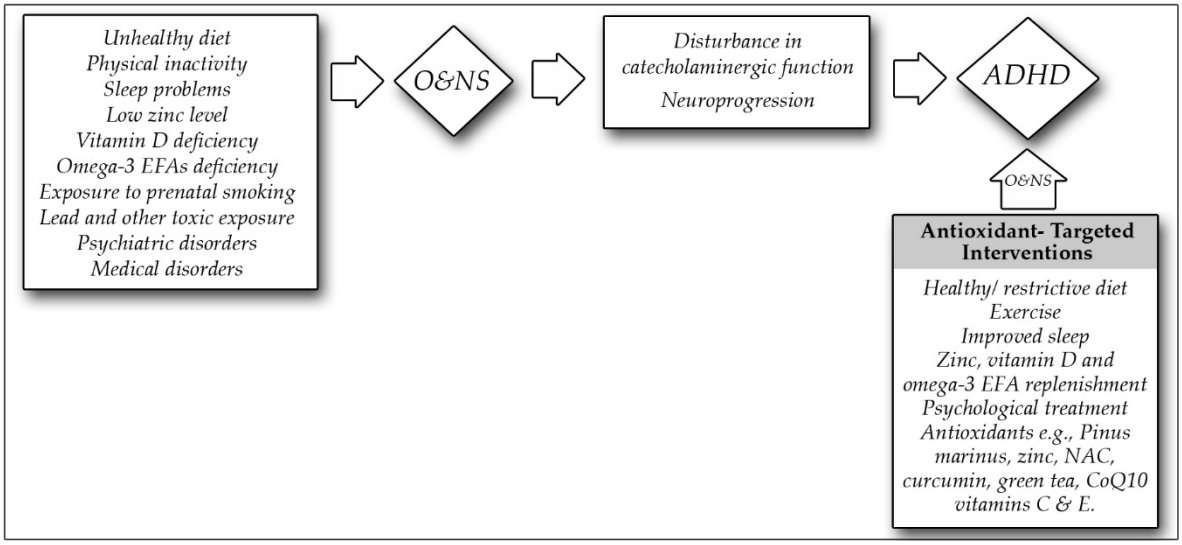

Figure 1. A theoretical summary of the effects of O&NS in ADHD and the potential role for antioxidant-targeted interventions. Increased O&NS is observed in ADHD which may be caused by an array of lifestyle, environmental, nutritional, psychological and medical factors. Compromised brain structures and catecholaminergic neurotransmission observed in people with ADHD are theorised to at least be partly caused by the detrimental effects of O&NS. If O&NS is causally related to ADHD, interventions that reduce O&NS present as potential treatments options for ADHD.