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Review on the oxidative stress in methamphetamine addicts

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ABSTRACT

A lot of research has found that there are toxic effects on the body and mental state at both the near- and long-term levels of addiction to methamphetamine. Therefore, the study of the chemical molecules that cause tissue damage in addicts is an important necessity to understand the mechanism of poisoning and open prospects for treatment. In this research, changes in oxidative stress molecules were reviewed in methamphetamine addicts.

The published papers that dealt with changes in oxidative stress final products, its enzymes, and antioxidants in addicts were reviewed, and the explanations reached by previous research were collected. It is concluded from this review that methamphetamine abuse causes an increase in the end-products of the generation of free radicals from the metabolic processes accompanying the biotransformation of methamphetamine and a decrease in antioxidants, which requires therapeutic intervention to reduce the harmful effects of methamphetamine abuse.

Keywords: *Review, Papers, Generation, Research*

INTRODUCTION

Methamphetamine (Meth) abuse/dependence is a worldwide public health issue linked to a rise in overdose mortality (Ahmad FB 2022) or death form the consequences of Meth intake (Faraone, Hess, and Wilens 2019). The widespread usage, high prevalence, and increasing overdose-related fatality rates make Meth the most widely abused substance in the world after cannabis (Jones et al. 2022; Hogarth, Manning, and van den Buuse 2021). Acute methamphetamine binges produce diffuse neuronal damage, which compromises dopaminergic signaling; however, the ramifications of chronic, low dose exposure and the processes through which methamphetamine causes damage to the cardiovasculature and periphery are ambiguous (Barr et al. 2006; Melega et al. 2008).

Therefore, the examination of the lipid profile and atherogenic indices are important for early detection and treatment of cardiovascular disorders. Methamphetamine users are a high-risk population for psychosis, not only because they are at risk of developing a methamphetamine-induced psychosis but, as a drug-using population, they are more likely to suffer from schizophrenia and other psychotic disorder (Arunogiri et al. 2020). Methamphetamine associated psychosis (MAP) represents a mental disorder induced by chronic methamphetamine use in a subset of users results suggest (Yang et al. 2021). that clear biological and clinical differences appear between patients presenting with MAP and schizophrenia and that there may exist distinct subgroups within MAP itself MAP specific treatment studies have been few and have focused on the use of antipsychotic medication

(Ewen, Potter, and Sweeney 2021). Advanced-glycated end-products (AGEs) result from non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids. AGEs and their transmembrane cell receptor (RAGE) have been involved in the pathophysiology of cardiovascular and metabolic diseases (Prasad 2014). Meth is chemically similar to dopamine and norepinephrine and readily crosses the blood/brain barrier, it produces its effects by causing dopamine and norepinephrine to be released into the synapse in several areas of the brain (Halpin, Collins, and Yamamoto 2014). Meth could alter the production of both inflammation and anti-inflammation components (Vargas, Rivera-Rodriguez, and Martinez 2020; Shafahi et al. 2018). Meth is present and sold in the illegal markets in basically three different forms including powder Meth (known as 'speed', has a lesser potent), base Meth, (known by various terms, including 'pure', 'paste', and 'wax', has a higher potency and purity than powder, and Crystal methamphetamine (known as 'ice', the most potent form) (Sutherland 2022). MA dependence and dosing explained together 44.7% of the variance in the OSTOX/ANTIOX ratio (Al-Hakeim et al. 2022a). The severity of dependence and MA dose were strongly correlated with increased sRAGE concentrations. Increased AGE-RAGE stress was strongly associated with OSTOX, OSTOX/ANTIOX, and MA-induced intoxication symptoms, psychosis, hostility, excitation, and formal thought disorders (Al-Hakeim et al. 2023).

METHODS

A literature search was performed using PubMed, Scopus, Medline, Embase, and the Cochrane database systematic reviews. Keywords used as search terms were addiction", "methamphetamine", "oxidative stress", "catalase", "myeloperoxidase", "glutathion peroxidase", "advanced oxidation protein products", "hydroxyguanine", "total antioxidant capacity", "nitric oxide". In our analysis, we did not place any restrictions on how long the evaluation may take. The database only includes articles written in English. To be included, research has to have examined the link between Meth addiction and one of the parameters.

Addiction

The definition of addiction under the Brain Disease Model (BDM) is as follows: "Drug addiction is a brain disease that develops over time as a result of the initially voluntary behavior of using drugs (Sinclair-House et al. 2020). The consequence is virtually uncontrollable compulsive drug craving, seeking, and use that interferes with, if not destroys, an individual's functioning in the family and in society (Goldberg 2020; Perales, King, Navas, Schimmenti, Sescousse, Starcevic, van Holst, Billieux, et al. 2020). There are at least two pathways through which positively or negatively reinforcing activities can become dysregulated and eventually problematic: domain-specific compulsivity and relative outcome utility computation (Perales, King, Navas, Schimmenti, Sescousse, Starcevic, van Holst, and Billieux 2020). Meth addiction involves physical and psychological addiction (dependence) (Halkitis 2009). Methamphetamine use disorder is a chronic neuropsychiatric disorder characterized by recurrent binge episodes, intervals of abstinence, and relapses to drug use (Guerin et al. 2021). It has been found that Meth use increased the severity of a range of psychiatric symptoms (Stuart et al. 2020). Symptoms of depression and anxiety are particularly common in this group, and have been reported when regularly using Meth and at higher rates during abstinence (Kuitunen-Paul et al. 2021). Symptoms exacerbated by Meth use clustered on three dimensions: positive psychotic symptoms, affective symptoms and psychomotor agitation (Voce 2021). Meth results in fatigue, irritability, disturbed sleep, exhaustion, and symptoms of depression and anxiety, which might last for months (Zhao et al. 2021).

Oxidative Stress Of Methamphetamine

"Oxidative Stress" is defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage" (Sies, Berndt, and Jones 2017; Pisoschi et al.

2021). ROS, highly reactive molecules due to the presence of unpaired electron, are widely generated in eukaryotic cells as a result of incomplete, one electron reduction of O2 in mitochondria. Uncoupled transfer of electron from complex I and III in the electron transport chain (ETC) leads to formation of superoxide radical (O2-), which is a primary member of ROS (Ramalingam and Rajaram 2021). In the presence of O2 and transition metal ions, H2O2 can generate OH· via the Fenton reaction (Halliwell and Gutteridge 2015). Also, the Haber–Weiss reaction generates OH· from H2O2 and superoxide O2·− catalyzed by iron ions. Then, it was proven that the Haber–Weiss and Fenton reactions together were the main sources of radicals responsible for oxidative stress and cellular damages (Gulcin 2020).

Fe2++ H2O2 →Fe3+ + OH− + OH· (Fenton reaction).

O·2- + H2O2 → O2 + H2O + OH· (Haber−Weiss reaction).

OS may be of profound biological relevance with the AD (Butterfield and Mattson 2020). The ROS causes non-enzymatic chemical modification of a given biomolecule (e.g. lipid, protein, DNA) to produce the end-products of the molecules oxidation (Pisoschi et al. 2021). Meth disrupts energy metabolism by causing changes in gene expression and proteins associated with muscular homeostasis/contraction, maintenance of oxidative status, oxidative phosphorylation, and iron and calcium homeostasis (Sun et al. 2011). Furthermore, There is a high thiol/disulphide homeostasis (another OS marker) in Meth use disorder (Hacimusalar et al. 2019). ROS and RNS are products of normal cell metabolism and have either beneficial or deleterious effects, depending on the concentration reached in the tissues (Xu et al. 2021). Three clusters were formed with a silhouette measure of cohesion and separation of 0.62. These included healthy controls (n = 30) and individuals with lower psychotic symptoms and oxidative stress (MA-PSO, n = 30) versus those with high psychotic symptoms and oxidative stress (MA+PSO, n = 30). PCs is able to extract from SDS1 (loading = 0.913), SDS2 (0.951), SDS4 (and 0.691), and SDS5 (0.878) (KMO = 0.832, Bartlett's test chi-square = 287.09, df = 6, p < 0.001, AVE = 0.747, labeled PC_SDS). It's also able to extract a validated PC from PC_SDS (0.959), dosage (0.854), MA use last month (0.961) and route of administration entered as an ordinal variable (0.672) (KMO = 0.743, Bartlett's test chi-square = 367.85, df = 6, p < 0.001, AVE = 0.756, labelled: PC_MA) (Al-Hakeim et al. 2022b).

Enzymes Of Oxidative Stress

Several enzymes obstruct free radicals' formation, some of them act directly in scavenging ROS (primary enzymes), whereas "secondary enzymes" play an indirect role by supporting other endogenous antioxidants (Amir Aslani and Ghobadi 2016). Superoxide radical anion can be transformed by enzymes belonging to the superoxide dismutase family, which deplete superoxide anion radicals occurring from the action of extracellular factors (including ionizing radiation and oxidative impairments), or from oxygen metabolism, in the electron transport chain Hydrogen peroxide can be generated by any system yielding superoxide, as the radical anion readily disproportionates (Hou, Zeng, and Zhang 2020). The presence of oxidases (urate oxidase, glucose oxidase, D-aminoacid oxidase) can result in direct hydrogen peroxide synthesis by two electron transfer to molecular oxygen (Waldeck-Weiermair et al. 2021).

Catalase (EC 1.11.1.6)

Catalases play a remarkable role in detoxifying H2O2 under stress conditions. H2O2 is an initial molecule involved in defense response leading to production of further defensive components (Sandhu, Sarao, and Sharma 2020). Primary enzymes act directly on the main ROS arising from incomplete O2 reduction, O2– and H2O2. SOD scavenges the O2–, whereas CAT and glutathion peroxidase (GPX) remove the H2O2. SOD (E.C. 1.15.1.1) is a metalloenzyme, catalyzing superoxide anion dismutation to H2O2 and molecular oxygen, as shown in reaction 1 (Singh et al. 2017). The activities of the erythrocyte antioxidant enzymes GPx, CAT, and SOD were significantly decreased (-32%, -14% and -31%, respectively) in amphetamine users (Govitrapong et al. 2010). The activity of

SOD and CAT enzymes and GSH content were reduced (Ahmadi and Foruozandeh 2020). This result is consistent with the ability of Meth to generate H2O2 and NO species from various sources, including dopamine oxidation and glutamate-induced NO synthase (NOS) activation (Krasnova and Cadet 2009) . At baseline, the recently abstinent METH abusers had significantly higher MDA levels, lower SOD activity, and higher CAT activity and GSH levels compared to healthy controls. CAT and GSH values were positively correlated with MDA but negatively correlated with SOD (Huang et al. 2013). In addition, Meth caused decrease in catalase (CAT) activity in the striatum of non-Tg mice (Jayanthi, Ladenheim, and Cadet 1998a).

Myeloperoxidase (MPO)

Myeloperoxidase (MPO, EC 1.11.1.7) is a hemoprotein expressed in azurophilic granules of neutrophils and in the lysosomes of monocytes (Haegens et al. 2009), then releases MPO into the phagolysosome or into the extracellular space in response to a variety of agonists (Nauseef 1998). The neutrophil MPO activity may also contribute to O2 deprivation in these patients, rationalizing the phenomenon of patients with relatively low oxygen saturation without corresponding symptoms (Goud, Bai, and Abu-Soud 2021). MPO is a strong oxidant stored in primary granules of neutrophils with potent antibacterial and proatherogenic properties by generating a potent oxidant, HOCl (Park et al. 2013). The enzyme has strong antibacterial properties and is unique in its ability to generate potent bactericidal compounds such as HOCl from hydrogen peroxide and the halide, chloride (Pahwa, Modi, and Jialal 2022). MPO participates in innate immune defense mechanism through formation of microbicidal reactive oxidants and diffusible radical species, A unique activity is its ability to use chloride as a co-substrate with hydrogen peroxide to generate chlorinating oxidants such as HOCl, a potent antimicrobial agent (Soubhye et al. 2021). Elevated MPO levels in circulation are associated with inflammation and increased oxidative stress (Ndrepepa 2019). MPO may lead to irreversible protein and lipid modification, increasing levels of oxidized low-density lipoprotein, and promoting atherogenesis. It is an antimicrobial enzyme found in neutrophils and PMNs (Karahocagil et al. 2012). Irreversible inhibitors will form strong, covalent bond with iron atom of the heme center, thus efficiently blocking H2O2 from accessing active site and rendering enzyme inactive (Galijasevic 2019).

Glutathion Peroxidase (EC 1.11.1.9)

Glutathion Peroxidase (GPX) (E.C. 1.11.1.19) is a selenium-dependent oxidoreductase, which uses H2O2 or organic hydroperoxide as the oxidant, and the tripeptide GSH as the electron donor (Cardoso et al. 2017). An incoming second GSH molecule attacks Enz-Se-SG, regenerating the enzymatic resting form Enz-SeH, releasing the oxidized and dimerized GSSG (Cardoso et al. 2017). GPx is a selenium-dependent enzyme, GPX, the main enzyme of the GSH antioxidant system, reduces OS species such as lipid peroxidation products (Flores-Mateo et al. 2009). GPx is upregulated in response to OS challenge because it is the major antioxidant protein (Espinosa-Diez et al. 2015). GPx acts in co-ordination with other signaling molecules to exert its own antioxidant role (Sharma, Shin, Sharma, Nah, Mai, Nguyen, Jeong, Lei, and Kim 2021). GPx is the general name of an enzyme family with peroxidase activity. It protects cells from oxidative damage through decreasing lipid hydroperoxides to their corresponding alcohols or reducing free hydrogen peroxide to water (Zedan et al. 2015). It has a protective effects on various neurodegenerative disorders (i.e., Parkinson's disease, Alzheimer's disease, cerebral ischemia, and convulsive disorders) (Sharma, Shin, Sharma, Nah, Mai, Nguyen, Jeong, Lei, Kim, et al. 2021). Meth induced oxidative cell stress by increasing MDA while decreasing cell GSH and the antioxidant enzymes such as CAT and GPx levels. Meth induced DNA damage and proteins disappearance in brain, liver and kidney tissues (Koriem, Selim, and Mazen 2021). Glutathione (GSH) and GSH/glutathione peroxidase (GPx) enzyme system is essential for normal intracellular homeostasis and gets disturbed under pathophysiologic conditions including endothelial dysfunction. Overproduction of reactive oxidative species (ROS) and reactive nitrogen species (RNS)

including superoxide (O2•−), and the loss of nitric oxide (NO) bioavailability is a characteristic of endothelial dysfunction (Panday, Talreja, and Kavdia 2020). A significant reduction in the activity of GPx and catalase was observed after Meth treatment. A decrease in GPx activity may have been partially due to diminished GSH levels that GPx needs as a substrate. We previously reported decreased GPx activity, due to Meth, in human brain microva- scular endothelial cell culture (Bradford 1976).

End products of oxidative stress

The formation of ROS is an inevitable byproduct of metabolism (Huang and Li 2020). The main source of ROS in mammalian cells is the "dripping" of electrons from the mitochondrial respiratory chain, and their subsequent transfer to molecular oxygen, resulting in the formation of the superoxide anion (O2•) (Saxena et al. 2021). H2O2 is able to produce highly reactive radicals as a result of its interaction with metal ions In this group enzymes are also found, which bind redox-active metals—iron is the most important transition metal in mammalian cells—in an inert form (Maret and Medicine 2019). The main end-product of the lipid peroxidation is malondialdehyde (MDA), which may lead to cell damaging, reacting with the free amino groups of proteins and nucleic acids, with the target mutagenic activity at the site of guanine in the DNA sequence (Štefan et al. 2007; Salzman et al. 2009). The increase of MDA and 4-hydroxynonal in different brain regions of Meth users has reported early (Fitzmaurice et al. 2006). MDA is one of the most commonly investigated markers of lipid peroxidation, might assist with the monitoring of oxidative balance in OSA (Pau et al. 2021). MDA within a lipid pathway has been demonstrated to possess an important role in endothelial function that undergoes periodontitis and coronary heart disease (CHD) development (Isola et al. 2019). MDA is the most extensively investigated of these products because of its reactivity with a range of biological macromolecules and its association with the pathophysiology of a number of disease states. MDA is formed enzymatically as a product of the cyclooxygenase reaction in prostaglandin and thromboxane synthesis (Draper et al. 2019). Acute Meth binges produce diffuse neuronal damage, which compromises dopaminergic signaling; however, the ramifications of chronic, low dose exposure and the processes through which Meth causes damage to the cardiovasculature and periphery are ambiguous (Barr et al. 2006; Melega et al. 2008).

Advanced oxidation protein products

Advanced oxidation protein products (AOPP) are derived from oxidation-modified albumin (its aggregates or fragments), but also of fibrinogen, and lipoproteins. Oxidative stress (OS) is the main element in this modification and the most significant is the myeloperoxidase/H2O2/halide system (Celi and Gabai 2015). Physiologically, AOPP are formed during the whole life in small quantities and increase with age. Significantly higher concentrations of AOPP are observed in many pathological conditions, also in diabetes. In diabetes the formation of AOPP is induced by intensified glycooxidation processes, oxidant-antioxidant imbalance, and coexisting inflammation (Piwowar 2010). Evidence suggests an imbalance between antioxidant and oxidant-generating systems resulting in oxidative stress in uremic patients. As plasma proteins are critical targets for oxidants, we developed a novel spectrophotometric assay which allows to detect advanced oxidation protein products (AOPP) in uremic plasma (Witko-Sarsat et al. 1996). Advanced oxidation protein products (AOPPs) included dityrosine- and cross-linking protein products, which are considered as novel markers of oxidative stress (Škvařilová et al. 2005). The role of AOPPs in the activation of NADPH oxidase has been described previously, and is regarded as the major source of ROS generation. However, the mechanism of ROS generation triggered by AOPPs in the pathophysiology of SCI has not yet been studied (Zheng et al. 2013). High levels of nitro-oxidative stress (NOS) are confirmed in schizophrenia as indicated by increased reactive oxygen (ROS) and nitrogen species (RNS), increased lipid peroxidation as indicated by increased levels of lipid hydroperoxides, and increased protein oxidation as indicated by increased advanced oxidation products (AOPP), and lowered total antioxidant

defenses (Maes et al. 2020). Therefore, we hypothesized that indicants of increased oxidative stress toxicity (OSTOX) and decreased antioxidant defenses (ANTIOX) may be detected in patients with MA dependence and MIP during MA intoxication. Nonetheless, no studies have reported associations between OSTOX/ANTIOX and MIP in MA-dependent individuals during MA intoxication. Hence, the aim of the present study is to examine whether MA dependence and MIP during intoxication are characterized by (a) increased serum NOS/OSTOX biomarkers, including malondialdehyde (MDA), myeloperoxidase (MPO), nitric oxide (NO), oxidized high-density lipoprotein (oxHDL) and low-density lipoprotein (oxLDL) levels; and (b) lowered ANTIOX biomarkers, including catalase-1, glutathione peroxidase (Gpx), total antioxidant capacity (TAC), HDL cholesterol, and zinc.

hydroxyguanine

One of the most prevalent DNA lesions generated by reactive oxygen species is 8-hydroxy-di-guanine (8-oxo-Gua). This can result in adenine-incompatible pairings on the genome, such as G to T and C to A (Kroese and Scheffer 2014). This imbalance results in increased levels of intensified oxidative and nitrosative stress biomarkers, such as 8-hydroxyguanine (8-oxoG), 8-iso prostaglandin F2a (8-iso-PGF2a), malondialdehyde (MDA), and NO (Stefanescu and Ciobica 2012; Yager, Forlenza, and Miller 2010). The substantia nigra is known to undergo intense peroxidative stress, showing a considerable increase in levels of such oxidative markers as peroxidised lipids (Dexter et al. 1989). 8-hydroxyguanosine (a marker of oxidative stress to DNA),(Alam et al. 1997). Substantial evidences have shown that mitochondrial dysfunction plays a key role in the accumulation of toxic reactive oxygen species that leads to insulin resistance (Hesselink, Schrauwen-Hinderling, and Schrauwen 2016; Nakanishi et al. 2004). In DNA, the hydroxylation of guanine by ROS at the 8-position, the 8-hydroxylation of guanine, leads to the lack of specific base pairing and misreading of the modified base and adjacent residues. When this occurs, extensive and specific repair is performed by the cell for survival and to maintain genomic integrity (Chiou et al. 2003). One of the ROS-caused DNA lesions is an oxidized form of 8-hydroxyguanine (8-OHG) known as 8-OHdG which can be used as a DNA damage biomarker. For PD patients a rise for 8- OHdG serum levels was also assessed compared to normal individuals (Shigenaga, Gimeno, and Ames 1989).

Antioxidant Of Methamphetamine

An antioxidant is a molecule capable of inhibiting the oxidation of other molecules (Gulcin 2020). ROS occur in living organisms during normal cellular metabolism and can be harmful decisive biomolecules including lipids, carbohydrates, nucleic acids, and proteins (Cakmak and Gülçin 2019). Living organisms including the human body can protect themselves by scavenging ROS and producing endogenous or exogenous antioxidant compounds that scavenge free radicals (Hamad et al. 2017; Anraku et al. 2018). Due to the highly reducing cellular environment, powerful antioxidative systems are needed, that are capable of scavenging ROS or transforming them into less reactive products (Sablas et al. 2020). These compounds help in scavenging the species that initiate the peroxidation, breaking the autoxidative chain reaction, quenching (•O2-), and preventing the formation of peroxides The most effective antioxidants are those possessing the ability to interfere with the free radical chain reaction (Hu et al. 2020). Antioxidant agents include molecules such as glutathione or ascorbic acid and antioxidant enzymes (AOEs) such as CAT, SOD or GPx (Bratovcic 2020). Only when the antioxidant capacity of the cell is overwhelmed, can ROS exert their damaging potential (Li et al. 2020). The redox imbalance is more likely triggered by the net effect of low antioxidative defense systems and incessantly produce of reactive species, including O2-, •OH, peroxynitrite (ONOO-), hydrogen peroxide (H2O2), reactive lipid aldehydes, and reactive nitric oxide (NO) (Kükürt et al. 2021). Antioxidants control the autoxidation by interrupting the propagation of free radicals or by inhibiting the formation of free radicals via

different mechanisms (Di Meo, Venditti, and longevity 2020).

Total Antioxidant Capacity (TAC)

The total antioxidant capacity (TAC) is a measure of the amount of total antioxidants in blood that provides an assessment of several antioxidants in samples (Jaberie, Momeni, and Nabipour 2020). The concept of "total antioxidant capacity" (TAC), which originated from chemistry and then was applied to biology and medicine, and further to nutrition and epidemiology, needs critical appraisal, because there are serious limitations that preclude meaningful application to in vivo conditions (Sies 2007). TAC is the measure of the amount of free radicals scavenged by a test solution (Ghiselli et al. 2000), being used to evaluate the antioxidant capacity of biological samples (Marques et al. 2014; Bartosz 2010; Pinchuk et al. 2012). TAC is an analyte frequently used to assess the antioxidant status of biological samples and can evaluate the antioxidant response against the free radicals produced in a given disease (Rubio et al. 2016). As free radicals are produced, plasma TAC induction occurs to scavenge them. Malnutrition in chronic abusers of Meth results in depletion of plasma TAC in comparison with healthy subjects (Werb et al. 2010). Meth-dependent patients had significantly lower TAC relative to controls (Walker et al. 2014). In a previous study, plasma TAC was found to be lower in blood samples of Meth dependent patients than in those of healthy controls (Walker et al. 2014). METH toxicity is also supported by reports that the drug can reduce the levels of antioxidant enzymes (Jayanthi, Ladenheim, and Cadet 1998b), increase lipid peroxidation and cause the formation of protein carbonyls (Gluck et al. 2001).

Nitric oxide (NO)

Nitric oxide (NO) is a free radical playing an important pathophysiological role in cardiovascular and immune systems (Fang et al. 2021). NO is synthesized from l-arginine through the action of the nitric oxide synthase (NOS) family of enzymes, which includes three isoforms: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS) (Anavi and Tirosh 2020). NO produced by iNOS is essential for the normal inflammatory response, while dysregulation of iNOS is implicated in a variety of chronic and acute diseases. Recent advances in structural characterization and new insights into regulation of iNOS expression have allowed the design and development of highly selective and potent iNOS inhibitors (Cinelli et al. 2020). The signaling functions of nitric oxide are accomplished through two primer mechanisms: cGMP-mediated phosphorylation and the formation of S-nitroso cysteine on proteins (Tenopoulou and Doulias 2020). Exercise should be recommended for increasing the level of NO for athletes and for patients with cardiovascular disorders for therapy (Oral 2021). Nitrosylation of tyrosine (Tyr) leading to 3-nitrotyrosine proteins or free 3-nitrotyrosine is the most prominent change (Ischiropoulos 2009).

CONCLUSION

The findings of this review lead us to the conclusion that abusive use of methamphetamine leads to an increase in the end-products of the generation of free radicals from the metabolic processes that accompany the biotransformation of methamphetamine and a decrease in antioxidants. As a result, therapeutic intervention is required in order to reduce the negative effects of abusive use of methamphetamine.

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