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Impact of the Drug Addiction on Oxidative Stress

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Abstract

Drug addiction is a chronic, recurrent mental illness marked by compulsive drug seeking despite grave adverse effects. Methamphetamine (METH) is a member of the synthetic drug class known as amphetamine-type stimulants, a class of medications that stimulate or create alertness and behavioural activation as well as increased central nervous system activity. There is an imbalance between free radical production and the body's ability to neutralise reactive intermediates by neutralising antioxidants, which causes oxidative stress. METH causes a significant increase in the oxidation of dopamine (DA), which results in the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). The body is protected by antioxidants, which can lessen ROS/RNS damage. By preventing reactive radicals from forming or by halting free radical reactions, the protective system's function may reduce the harmful consequences of free radicals. The goal of the current review was to draw attention to the impact of drug addiction (namely, METH) on oxidative stress in humans and the value of employing natural antioxidants to mitigate the harm that results. As a result of drug misuse, including METH usage, neuronal damage result from oxidative stress within mitochondrial membrane and DA pathway. Vitamin C, E, and other natural compounds have been found as being particularly promising in terms of their effects and safety.

Keywords: Drug Addiction; Amphetamine; Oxidative Stress; Methamphetamine; Antioxidants.

1. Introduction

1.1. Drug addiction

Drug addiction or substance can be defined as a chronically relapsing disorder, characterised by compulsion to seek and take the drug, loss of control in limiting intake, and emergence of a negative emotional state (eg, dysphoria, anxiety, irritability) when access to the drug is prevented. The term "addiction" is now used to refer to substance use problems from a diagnostic view [1,2].

Drugs can be classified in three ways: behavioural, pharmacodynamic, and legal classification. The behavioural classification includes six main categories: stimulants, opioids, sedative hypnotics, antipsychotics, antidepressants, and psychedelics. In addition, pharmacodynamic classification describe the pharmacodynamic effects on brain neurotransmission (Table1). While, the legal classification involves two categories: prescription vs. nonprescription and drug abuse [3].

Table 1: Behavioral and Pharmacodynamic Classification of Psychotropic Drugs [3].

Drug Class	Behavioral	Pharmacodynamic (Neurotransmitters)
	Stimulants Caffeine, Nicotine, Cocaine, Methamphetamine	Dopamine
	Opioids Morphine, Heroin, Meperidine (Demerol)	Enkephalins Endorphins
	Sedative hypnotics Alcohol, Diazepam (Valium)	Gama-Aminobutyric Acid GABA
	Antipsychotics Haloperidol	Dopamine
	Antidepressants Fluoxetine (Prozac)	Norepinephrine Serotonin
	Psychedelics Lysergic acid diethylamide, Psilocybin, Marijuana	Serotonin Glutamate Endocannabinoids

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1.2. Stimulants

A class of medications known as psychostimulants/stimulants that stimulates or produces arousal and behavioural activation while also increasing central nervous system activity. Due to their extensive pleasant and reinforcing effects, they are widely used as creational drugs and develop into important drugs of abuse. Amphetamine-type stimulants include Methamphetamine(METH), amphetamine, methylenedioxy-methamphetamine, and methylenedioxy-methamphetamine (MDMA) [4]. N-methyl-1-phenylpropane-2-amine, also known as METH, is a highly synthetic drug that causes dependence and has a fundamental impact on the brain's neurotransmitter systems. It causes sensations of euphoria, vigor, and alertness [5]. Regarding its pharmacodynamic effects, METH is comparable to amphetamine; however, because of its higher penetration into the central nervous system (CNS) and longer duration of action, METH users are more prone to develop an addiction to it [6]. The METH usage results in severe bodily and mental harm over time [7].

1.3. Cycle of addiction

When impulsive drug use turns into compulsive drug use, this is called a "vicious cycle" of changes in the brain and behaviour [1,8].

1.3.1. Binge/intoxication stage:

Impulsively administering drugs can trigger the brain's reward system, which may drive drug users to relapse. The mesocorticolimbic dopamine (DA) system's consuming stage is hypothesised to depend on DAergic connections from the ventral tegmental area (VTA) to the hippocampus (HIP), prefrontal cortex (PFC), and nucleus accumbens (NAc) [9].

1.3.2. Wthdrawal / negative affect stage:

A negative withdrawal symptom eventually replaces the positive reinforcement after repeated drug use thanks to the development of adaptive tolerance. The onset of the withdrawal stage is accompanied by the hypothalamic-pituitary-adrenal (HPA) axis becoming overactive, which causes the production of corticotropin-releasing factor (CRF) in the A mygdala (AMY), prefrontal cortex (PFC), and VTA. This leads in a number of withdrawal syndromes [10].

1.3.3. The preoccupation/ anticipation stage:

While abstainers who have stopped using drugs are more likely to relapse when exposed to the drug prime, stress, or drug signals again [1]. The PFC, HIP, and AMY activate glutamatergic (Gluergic) neurotransmission that goes through VTA and releases CRF in the bed nucleus of striaterminalis (BNST), and it is thought that this is what causes DA overflow in the NAc during this period [10-12] (*Figure1*).

2. Neurotransmitters

Endogenous chemical messengers known as neurotransmitters are in charge of facilitating neuronal transmission throughout the body. By facilitating what is known as chemical synaptic transmission, these substances help the central nervous system govern a number of different activities. There are over 50 neurotransmitters in the brain, including amino acids, amines, purines, peptides, and certain gases. The term "neurotransmitter" should only refer to a substance that conducts chemical messages between neurones inside the confines of the synapse, a unique structure. Either inside the cell or on the cell surface, the receptors might be found. In order for a neurotransmitter to connect to a cell surface receptor, the activity of an effector system must change as a result of the binding, which then changes the concentration of an intracellular messenger [14,15].

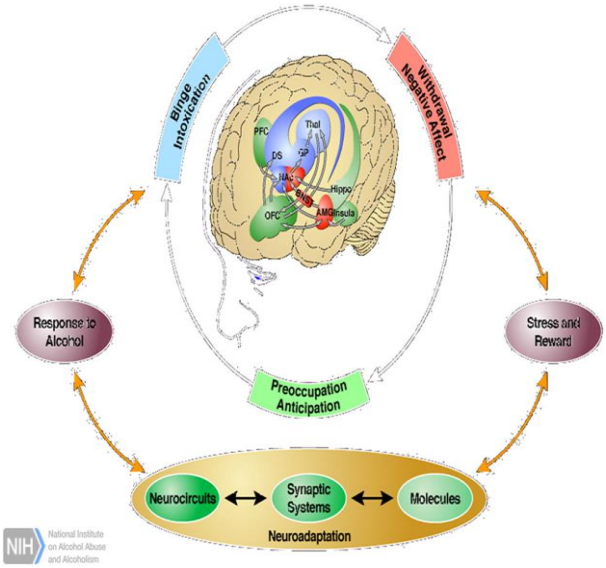

Fig 1: Neurobiological underpinnings of the development of substance use disorders conceptual framework [13].

2.1. Dopamine

There are a number of functions in the brain that are regulated by DA, including control over voluntary activity, reward and circadian rhythm as well as consciousness and cognition. L-tyrosine hydroxylase (TH) is responsible for the hydroxylation of L-tyrosine to Dihydroxyphenylalanine (DOPA), while aromatic L-amino acid decarboxylase (AADC) is responsible for the decarboxylation of DOPA to produce DA[16]. Several enzymes, including catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), are involved in the breakdown of DA into homovanillic acid (HVA) and 3,4-dihydroxyphenylacetate (DOPAC), respectively. The DA exerts its effects through two distinct subclasses of

DA receptors: dopamine1-like (D1 and D5) and dopamine 2-like (D2, D3, and D4). There are several functions regulated by DA receptors. These include growth and development; sleep; locomotion; emotions; renal functioning; gastrointestinal motility; and etc. It is also important to note that drug addiction, schizophrenia, anxiety, and Multiple Sclerosis (MS) are all conditions that affect the dopaminergic system. Moreover, Parkinson's disease (PD), Huntington's disease (HD), Alzheimers disease (AD), epilepsy, and other neurological conditions are also linked to the dopaminergic system [17,18].

2.2. Glutamate

The excitatory amino acid Glutamate (Glu) is a prevalent brain neurotransmitter. It is biosynthesized in the mitochondria from glucose-derived tricarboxylic acid (TCA) derivatives. Four enzymes are involved in glutamate neurotransmission, in which glutamate can serve as either a substrate or a product. Gutamate dehydrogenase, aminotransferase, glutamine synthetase, and glutaminase are the enzymes involved in glutamate's neurotransmission. When engaged, N-Methyl-D-aspartic acid (NMDA), amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and kainate are ionotropic glutamate receptors that allow ions to pass through membrane channels. While the NMDA receptor increases membrane permeability for calcium, the AMPA and kinate receptors increase membrane permeability for sodium and potassium. Although glutamate plays important roles as a neurotransmitter, it is also known for its toxicity to neurons, a phenomenon known as "excitotoxicity" that causes excessive firing of neurons in the brain and the emergence of brain disorders such as Huntington disease, progressive memory loss, cognitive decline (Alzheimer's disease), and progressive muscle weakness (amyotrophic lateral sclerosis) [19,20].

3. Oxidative Stress

Oxidative stress (OS) results from an imbalance between the biological system's capacity to detoxify reactive intermediates through the neutralisation of antioxidants and the generation of free radicals. Free radicals and peroxides can have harmful effects on the proteins, lipids, and DNA that make up a cell. The brain, the organs most severely impacted by oxidative stress, uses roughly 20% of inspired oxygen and produces more free radicals than any other organ in the body, although making up only 2% of the total weight. Addiction to drugs like amphetamines and METH causes OS, which leads to brain damage. Although the exact mechanisms by which free radicals harm neuronal tissue are not fully understood, it is well acknowledged that both the blood–brain barrier BBB permeability and the healthy architecture of the brain are impacted [21]. METH increased DA levels while also causing an increase in free radicals. It damages brain DA neurons by inducing dopamine-dependent OS and the production of free radicals, which have negative effects on lipid profiles and antioxidant enzymes. [22].

3.1. OS & Dopamine pathway

Dopamine, serotonin, and norepinephrine are the main neurotransmitters released by the psychostimulant METH. In the mesolimbic area of the brain, these neurotransmitters contribute to neuronal cell necrosis and inflammation. The METH increases the oxidation of DA, resulting in the production of ROS such as hydroxyl radicals $OH^{\cdot}$, hydrogen peroxide H_2O_2, and superoxide anion $O_2^{\cdot-}$. The mechanism of METH intoxication and the activation of DA release are intrinsically linked. Chronic METH usage inhibits DA release by primarily influencing plasma membrane dopamine transporters (DATs) and vesicle monoamine transporter-2 (VMAT-2) — two crucial components of the dopaminergic neuronal terminal [23,24].

Solubility of METH in fat permits it to quickly penetrate the BBB and reach the brain. Passive diffusion as well as the DAT are two ways in which it reaches dopaminergic terminals [25,26]. In order to regulate and maintain DA homeostasis, DATs extract DA from the extracellular area and absorb it into presynaptic dopaminergic neurons. The DA is generally released into synapses when neurons are stimulated. Drugs like as METH cause aberrant DAT trafficking, which boosts extracellular DA levels by inhibiting dopamine reuptake, increasing dopamine efflux, and internalising DATs from the plasma membrane. DATs-dependent dopaminergic neurons are stimulated by METH, as well. As a member of the Na^+/Cl^- dependent co-transporters, the DAT transports DA in both directions because of the Na^+/Cl^- ions' movements. METH increases the inward current mediated by DATs and boosts DA neurons' activity. By hindering the action of VMAT-2 and boosting DA release, METH dramatically raises the levels of DA in the cytosol and synaptic cleft. Monoamines are moved from the intracellular cytosol into synaptic vesicles via the membrane protein VMAT-2, which is a component of the membrane. But METH interferes

with the proton gradient that is mediated by the hydrogen pump, causing synaptic vesicles to release monoamines into the cytosol. Additionally, METH binds to VMAT-2 and limits monoamine uptake through a competitive process, causing the cytoplasm to contain high levels of monoamines. A large rise in DA levels in endogenous cells is also a result of the malfunction of VMAT-2 brought on by METH, which disrupts the physiological storage of DA. The neurotoxic effects associated with large dosages of METH can be attributed to DA levels that are so high they can easily pass through cells and cause considerable oxidative damage [27-29].

Excess DA is autoxidized to quinone or semiquinone in dopaminergic terminals and synaptic clefts, where it produces significant amounts of H_2O_2, OH-, and O_2^-. Additionally, H_2O_2 is a consequence of the minor amount of DA metabolism mediated by Catechol-O-methyltransferase (COMT) or monoamine oxidase (MAO). The very poisonous OH- is created when H_2O_2 interacts with transition-metal ions. There is an increase in OS when ROS levels are too high, which causes the cell death cascade to be activated. When antioxidative enzymes are missing, oxygen's highly toxic peroxynitrite ions $ONOO^-$, which are generated when oxygen combines with nitric oxide (NO), can destroy proteins, nucleic acids, and phospholipids in cells [30,31] (Figure2).

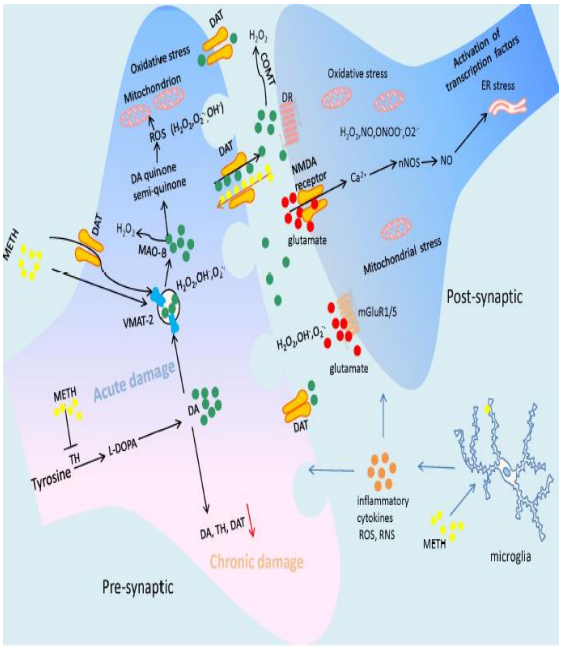

Fig 2: The illustration outlines the key methods through which methamphetamine (METH) causes neurotoxic effects [31].

3.2. OS & Mitochondrial dysfunction

Within neural cells, mitochondria are a significant source of METH-induced ROS generation [32]. Mitochondria are the cell's primary source of energy because of their role in oxidative phosphorylation and ATP generation. Part of the METH-induced dopaminergic neurotoxicity can be traced back to mitochondrial malfunction, which prevents Krebs cycle activity and increases OS via the electron transport chain (ETC). As a result, there is an oxidative/antioxidative imbalance in brain cells [26]. DA oxidation generates ROS and RNS, which then impair mitochondrial function, DNA structural integrity, and genetic information, all of which are directly inhibited by these complexes of the ETC [26,33]. As a result of electron leakage, METH's suppression of ETC components increases O_2 production. Defects in mitochondrial respiration can therefore result in the loss of neurons and neurodegenerative disorders.

3.3. OS & Glutamate

The finding that METH triggers Glu release in the brain lends support to the theory that Glu is a factor in the toxicity of METH. Glutamate, a significant excitatory neurotransmitter in the brain, has been implicated in the excitotoxicity brought on by METH [31]. Particularly, high concentrations of Glu by METH activate the metabolic Glu receptor (mGluR) and the N-methyl-D-aspartate receptor (NMDAR) [20]. Increased intracellular Ca^{2+} concentrations result from the Glu build up over stimulating several downstream signal transduction pathways linked to Ca^{2+} influx [34]. The Nitric oxide NO is produced more readily when cells produce too much Ca^{2+}, which stimulates NOS, protein kinases, and phosphatases. Endoplasmic reticulum (ER) stress caused by excessive NO production activates the apoptotic pathway, which leads to METH neurotoxicity [33]. Numerous investigations have shown that different neuronal nitric oxide synthase (nNOS) inhibitors can prevent the METH-induced depletion of monoaminergic axons. These data suggest that METH-induced neurotoxicity is mostly caused by a Glu/NO mechanism [31].

4. Antioxidant

Antioxidants are chemicals made by the defence mechanisms of different organisms to lessen the harmful effects of free radicals and chlorin. By preventing reactive radicals from forming or by halting free radical reactions, the protective system's

function may reduce the harmful consequences of free radicals. Enzymatic and non-enzymatic antioxidant systems, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), lipid-soluble vitamin E, carotenes, and water-soluble vitamin C, regulate the balance between ROS and antioxidants in the body [35,36].

4.1. Vitamin C:

Ascorbic acid, also known as vitamin C, is one of the most widely used antioxidants and has been demonstrated to be helpful in treating neurotoxicity brought on by METH use. It has been shown that vitamin C inhibits apoptosis *in vitro* by decreasing ROS levels and activating apoptotic-related molecules [37,38].

4.2 Vitamin E:

Other antioxidants commonly used include tocopherols. Anti-oxidative stress can be provided to the cell membrane by vitamin E, in particular alpha-tocopherol (vitamin E), by preventing peroxidation of the phospholipidic bilayer. The amount of lipid peroxidation-related malondialdehyde (MDA) produced can be reduced by doing this [39].

4.3. Selenium is a microelement used in supplementation that protects against free radicals, reduces OS markers, and restores the optimal glutathione (GSH/GSSG) ratio, according to *in vitro* researches [40].

Mood stabilisers, such as lithium and valproic acid, can be used as an alternative to regulating mitochondrial activity. In order to inhibit the release of cytochrome c and reduce the creation of proteins linked to apoptosis, these drugs are used [41]. More investigation is needed to identify compounds with the similar propensity to reduce RNS. Since METH causes hyperthermia, the mechanism of action has not been fully explored, but it is thought that the capacity to block NO production is what causes neuroprotection rather than a role in thermoregulation [42].

4.4. Melatonin Melatonin controls the quantity of Ca^{2+} inside cells, providing protection against oxidative damage [43].

Using naturally occurring compounds as antioxidants is a common trend in research. A number of natural compounds have also been discovered and highlighted. Effects and safety data suggest that these compounds hold great promise. Due to the fact that most studies on antioxidants are done *in vitro*, and only a few are done on animal models, this constraint is present in their mechanisms. For example, ascorbic acid, selenium and lithium are all antioxidants, but only a small number of studies have been done on animal models. Figure 3 depicts the various ways that have been used to explain antioxidant action.

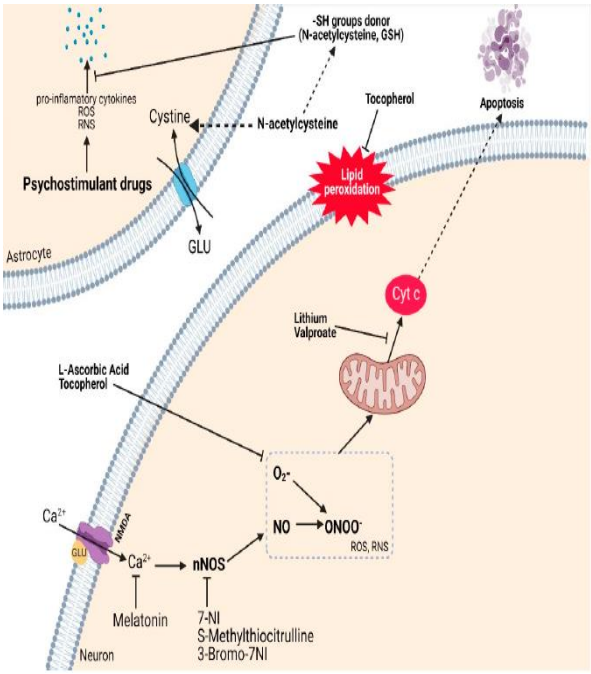

Fig 3: The mechanism of antioxidant therapy in drug-related toxicity is illustrated in this diagram. Reactive oxygen and/or nitrogen species (RNS), neuronal nitric oxide synthase (nNOS), and glutamate (GLU) [21].

5. Conclusion

As a result of drug misuse, including METH usage, neuronal damage result from OS within mitochondrial membrane and DA pathway. Vitamin C, E, and other natural compounds have been found as being particularly promising in terms of Their antioxidants effects and safety.

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