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Abstract

Substance use disorders (SUDs) can be defined as patterns of symptoms caused by the abusive consumption of recreational or prescribed substances that an individual continues to use despite their negative effects. Oxidative stress is one of the main pathophysiological processes occasioned by SUDs in different brain areas. Oxidative damage and subsequent deleterious symptoms can happen because of the consumption of psychoactive drugs, both stimulants and depressants. This chapter focuses on SUDs associated with depressant drugs, such as alcohol, opioids, benzodiazepines, and their effects on the central nervous system (CNS). We present the main characteristics of the SUDs and later explore endogenous mechanisms of repair, such as neuroglia and the endocannabinoid system. We also examine the neuroprotective effects of exogenous substances such as phytocannabinoids (e.g., cannabidiol) and N-acetylcysteine (NAC), which have shown important roles in anti-inflammatory pathways and antioxidative cascades, and how these molecules can be potential tools in the treatment of neurological symptoms of SUDs.

Keywords: oxidative stress, substance use disorder, depressant drugs, N-acetylcysteine, phytocannabinoids

1. Introduction

Oxidative stress is a concept introduced in the 1980s and is related to the imbalance or insufficiency of antioxidant systems to detriment of the production of reactive oxygen species (ROS) (Table 1), causing significant biological damage [1]. The production of ROS arises endogenously and exogenously. Cellular respiration is performed by mitochondria, in which there is a massive production of superoxide anion (O$_2^-$), (being one of the main endogenous sources of ROS) [2]. Activation of pro-inflammatory cytokines/chemokines exacerbated activation of the hypothalamic–pituitary–adrenal axis, and consequent mobilization of mineralocorticoid receptors are other examples of endogenous forms of ROS production. Furthermore, the environment, pollution, and drug consumption, such as alcohol and opioids, can exacerbate the process of free radicals' synthesis [3].
The central nervous system (CNS) is a highly susceptible site for oxidative stress process to occur once it demands a high consumption of O2 and nutrients, such as glucose and lactate. CNS contains a high content of fatty acids and lipid-rich structures, which also leads to increased oxidative stress [4]. High concentration of ROS can lead to increased blood–brain barrier permeability, decrease of synaptogenesis and neuroplasticity and can cause mitochondrial dysfunction, due to the processes of lipid peroxidation and protein oxidation caused by the binding of free radicals to primordial functional structures of the CNS [5].

To balance the production of ROS and free radicals in the CNS there are endogenous mechanisms of repair, such as the glutathione antioxidant system, which consists of the most abundant non-enzymatic antioxidant system (mainly responsible for the metabolism of peroxides and inactivation of free radicals) and some others, like neuroglia and the endocannabinoid system, which both will be discussed later in this chapter [6]. Alongside the endogenous mechanisms of repair, some exogenous molecules can be useful to reduce oxidative stress and subsequent damage. N-acetylcysteine or simply NAC plays a role in glutathione synthesis and shows prominent antioxidant properties. In addition, it has presented important therapeutic potential in the management of drug abuse [7, 8]. Moreover, recent studies have shown that phytocannabinoids, such as cannabidiol and Δ9-tetrahydrocannabinol (THC), presented antioxidant-like properties when involved in the regulation and balance of both prevention and recovery of damage caused by ROS and free radicals [9].

In this chapter, we will discuss about substance use disorders of depressant drugs, such as benzodiazepines, opioids, and alcohol, highlighting endogenous and exogenous mechanisms of repair and prevention of oxidative stress damage.

2. Substance use disorders: depressant drugs

2.1 Alcohol use disorder

Alcohol (ethanol) is one of the most consumed drugs in the world. Its consumption is related to the causes of 6–9% of all neuronal, mental, and substance use disorders [10]. Alcohol use disorder (AUD) is defined in DSM-V as a pattern of alcohol consumption that corresponds to two or more of 11 characteristics that an individual presented during a period of 12 months. These criteria can also be used for any other substance use disorder (SUD) [11].

In the U.S. alone, at least one-third of the population is likely to meet the criteria for AUD at some point in their lives [12]. It is well known that abusive ethanol

<table>
<thead>
<tr>
<th>ROS</th>
<th>Radicals</th>
<th>Non-Radicals</th>
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<tr>
<td>•O₂⁻</td>
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<tr>
<td>•OH</td>
<td>HOCI</td>
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<td>ROO•</td>
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Table 1. Main ROS produced in CNS.
consumption, including episodic binge drinking and more continuous pattern of drinking, can cause impairment in neuronal and cognitive aspects of individuals. Binge drinking, characterized by a heavy, fast, and episodic alcohol intake, is very popular among younger age groups. The prevalence of adolescents (15 to 19 years old) that consume alcohol in a binge pattern is similar to the overall population, with an almost 1:1 ratio in the Americas, Europe, and Western Pacific [13]. Likewise, binge drinking also presents potential damage to the brain, especially for adolescents and young adults, given that many areas of their brains are immature and still very plastic [14]. Although the impairments caused by AUD are explicit and abusive consumption of alcohol is a concern worldwide, studies are still needed to elucidate the consequences of alcohol consumption in the central nervous system (CNS).

So far, the action of ethanol in the brain is seemingly general and interacts with different areas and neuronal circuits, modulating the release of different neurotransmitters, such as GABA, glutamate, and dopamine. Nonetheless, alcohol has a widespread effect on the CNS; GABA receptors are the only ones known to have a binding site to ethanol, where it works as a positive allosteric modulator (Figure 1). This characteristic of the drug makes it even harder to specify its effects and mechanisms of action [16]. The higher levels of oxidative stress indicate a higher chance of developing memory impairments in several modalities, such as working, spatial and recognition memory; increase in anxiety levels, that can contribute to the onset of generalized anxiety disorder; reduced attention and decision-making skills, which can lead to future SUDs as well as impairment in social skills, even though alcohol is considered a social drug. Damage in the central nervous system caused by AUD is mostly regarded as an interrelation between oxidative stress and neuroinflammation promoted by neuroglia when microglia and astrocytes are activated.

The activation of microglia and astrocytes through neuroinflammatory process are modulated by the release of pro- and anti-inflammatory cytokines and other inflammatory mediators that also participate in the oxidative balance of the CNS. Microglial activation caused by abusive ethanol consumption raises the levels of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, as well as inflammatory mediators COX-2 and nitric oxide [15, 17–19]. The pro-inflammatory response to alcohol is mediated by toll-like receptors (TLR), in which the TLR-4 has an important role in both microglia and astrocytes. Given that acute ethanol effects on GABAergic signaling are mediated by TLR-4 [20], alcohol chronic consumption impairs the immune response through TLR-4 and can also lead to the development of neurological disorders, such as Alzheimer’s disease, demonstrating its key role in ethanol-related neurodegeneration [14, 21, 22]. Adolescent TLR-4 knockout mice did not raise alcohol preference over time when compared to control, as well as ethanol-induced levels of BDNF and Fos B in medial prefrontal cortex [23]. Thus, AUD appears to maintain and even escalate the ethanol intake, through the increase of glial inflammatory signaling, which in turn causes neurodegeneration and possible neuronal disorders [24].

Alongside the innate antioxidant and anti-inflammatory mechanisms, promoted by antioxidant enzymes, cytokines, and the glial cells, some exogenous and other endogenous substances are currently investigated as an alternative to neutralize neuronal damage caused by alcohol-induced oxidative stress. The endocannabinoid system (ECS) covers a vast area of the CNS and participates in the modulation of microglia inflammatory response, granting both phyto- and endocannabinoids an important role in alcohol-induced oxidative balance and neurodegeneration. Cannabinoid receptor type 1 (CB1) activation can lead to a reduction of
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Figure 1. Anatomical distribution of the main neurotransmitter systems that alcohol interacts with, with special attention to areas related to the symptoms presented in AUD. Ethanol, as a depressant drug, interacts with GABAergic synapses across the brain, whereas it also interferes with excitatory glutamatergic neurotransmission in the PFC and HC, altering synaptic and extra-synaptic glutamate transport [55]. In ST and the neuroanatomical complex SN/VTA, monoamines, such as dopamine and acetylcholine, and their receptors are also affected by alcohol consumption.
pro-inflammatory cytokines, iNOS, ROS, and higher protection from excitotoxicity, despite it being most expressed in neurons compared to glial cells [25–28]. Cannabinoid receptor type 2 (CB2) is more expressed in microglial cells. Thus, it is intrinsically involved in the regulation of the inflammatory response. Activation of CB2 is related to a decrease in the expression of pro-inflammatory cytokines, such as TNF-α, INF-γ, IL-1, IL-2, IL-6 and IL-12, iNOS, and chemokines [29–31]. It has been demonstrated that a chronic model of binge drinking in adolescent rats lead to an increase in levels of the enzymes that synthesize two important endocannabinoids (eCBs): anandamide (AEA) and 2-arachidonoylglycerol (2-AG), as well as pro-inflammatory mediators, such as TLR4, TNF-, COX-2 and GFAP in the medial prefrontal cortex (mPFC) [32].

The metabolic modulation of AEA (and other N-Acetyylethanolamines) by URB597, a FAAH selective inhibitor, prevented the production of ROS in both acute and chronic binge drinking models in adolescent rats [33]. Pretreatment with URB597 was able to prevent an increase of INF-γ and TNF-α levels in prefrontal cortex (PFC) and hippocampus in a chronic binge model in adolescent rats, as well as reduced IL-4, IL-10, and BDNF expression in PFC [34]. AEA also interacts with PPAR receptors, which are well known to modulate anti-inflammatory and antioxidant responses through the upregulation of NRF2, a transcriptional factor responsible to maintain redox homeostasis that inhibits oxidative stress and neuroinflammation [35]. Thus far, URB597 show to be a very promising neuroprotective substance against alcohol-induced oxidative stress and neuroinflammation.

N-acetylcysteine (NAC) is a promising, cheap, and accessible neuroprotective substance against oxidative damage caused by many SUDs, including AUD. In rodent models, NAC prevented the increase of pro-inflammatory and the decrease of anti-inflammatory cytokines in frontal cortex and hippocampus, and reduced leptin and corticosterone levels and hypoactive behavior after alcohol cessation in a chronic treatment [36, 37]. It also reduced motivation, seeking-behavior, and reacquisition in a model of ethanol self-administration [38]. NAC also reduced the anxiety-like behavior and oxidative stress levels in a withdrawal period after chronic ethanol exposure in zebrafish, with similar results obtained after acute exposure [7, 8]. Coadministration of NAC and acetylsalicylic acid provided some promising results on ethanol chronic intake and relapse, as this combination reduced both behaviors in rats. The synergism between these substances may act on the oxidative stress and neuroinflammatory cycle through different mechanisms, suggesting these cycles might contribute to relapse episodes and chronic alcohol consumption [39, 40].

2.2 Opioid use disorder

Opioid use disorder (OUD) refers to a problematic pattern of opioid use that affects 2 million people aged 12 or older in the United States, according to the 2018 national survey on drug use and health [41] that meet the DSM-5 criteria for OUD, while other 10 million misuse opioids—illegal or medically prescribed—in some degree [42].

OUD when regarded as the “opioid epidemic” is considered to be one of the most severe public health crisis in US history [38, 39], comprising at least four waves throughout the last decades, which have their own particularities when it comes to social, demographic, and health-related contexts [40, 41]. Over-prescribing licit pain relievers and low prices of street heroin and illicit fentanyl are examples of factors influencing the outspread consumption of opioids and subsequent OUD [42].
Diagnosis and evaluation of the severity of OUD in a given patient are assessed by the display of aberrant behaviors included as criteria in the DSM-5. Mild OUD is diagnosed by the presence of 2–3 criteria, while 4–5 criteria are considered moderate, and 6 or more are severe on the OUD spectrum [43].

Opiates, endogenous or exogenous, can act on three main receptors, but morphine and other alkaloid opioids have a high affinity for the receptor mu (μ), which is widely distributed in the brain. Receptor mu binding is responsible for the psychotropic effects of opioids, and eventual respiratory depression and death by overdose. Even though the vast majority of deaths as a result of illicit drug consumption are attributed to opioid use [44], it is important to notice that prolonged use of opioids and non-fatal overdoses are clinically significant, as they can lead to neurocognitive impairments [45, 46]. Oxidative stress has been demonstrated to be one of the main mechanisms of neuronal damage induced by licit and illicit opioids, as shown by studies in both animal and human subjects.

In rodent models, heroin can induce oxidative damage in the DNA, proteins, and membrane lipids in the brains of mice [47], while in rats, the repeated administration of licit pain reliever morphine is known to induce blood–brain barrier (BBB) disruptions during the withdrawal phase [48, 49] and this damage appears to be accentuated by oxidative stress [50]. Oxidative markers are also altered in the brains of Wistar rats exposed to codeine, another common pharmacologically relevant opioid [51].

One common trait in the incidence of brain oxidative stress after exposure to opioids (Figure 2) is that not only oxidative damage is noticed, but some endogenous antioxidant mechanisms are also impaired. The glutathione antioxidant system seems to be one of the most affected, as a decrease in both brain intracellular reduced glutathione (GSH) levels and glutathione peroxidase (GSH-Px) activity has been observed in mice [52]. In humans, post-mortem studies seem to suggest a similar pro-oxidant pathway, as reduced glutathione has been found decreased in the frontal, temporal, parietal and occipital cortex, brain stem, hippocampus, and white matter of deceased individuals with OUD that consumed heroin [53]. In mice brain, not only glutathione peroxidase activity was found impaired after heroin exposure, but also many other classic enzymatic antioxidant mechanisms, such as superoxide dismutase and catalase [54].

Therefore, secondary endogenous mechanisms of neuroprotection and repair are of great importance, as they can be potential targets for therapies aiming to manage OUD and subsequent oxidative damage caused by it. The endocannabinoid system has a well-known interaction with the opioid receptor system regarding anesthesia [55] and its role in the modulation of reward neural circuits have placed it as one of the most promising candidates for the non-opioid management of OUD [56, 57]. However, it is still not clear whether the endocannabinoid system could be further explored to counterbalance the deleterious pro-oxidative effects of OUD.

However, exogenous substances like NAC have demonstrated a lot of potential in treating OUD-associated oxidative damage. NAC is hydrolyzed after entering the cell and releases cysteine, a GSH precursor [58, 59]. As GSH levels are frequently impaired by OUD-induced oxidative stress, NAC appears as a frontrunner as a mitigator of ROS formation, as a consequence of opioid toxicity. Although the literature lacks more information regarding NAC-induced central neuroprotection against oxidative stress caused by OUD, in the periphery, NAC is capable of attenuating oxidative stress in the liver of tramadol-treated rats by stimulating the production of GSH [60].
2.3 Benzodiazepine use disorder

Benzodiazepines (BDZ) have been widely used anxiolytics since their development in the 1960s, comprising several drugs with anticonvulsant and sedative-hypnotic properties employed in various types of anxiety-related disorders. However, long-term treatment with BDZs is demonstrated to induce physiological dependence even in therapeutic doses, leading to increased anxiety and insomnia as a result of the withdrawal from the drug after months of use.

Therefore, there is a concern that most prescribed BDZs can potentially lead to drug abuse by former medical users and even nonmedical and recreational use by self-medication. In the United States, 6 million citizens in an age range starting from 12 years and older misused tranquilizers in 2016, making this class of drug the third most commonly misused illicit substance following marijuana (15%), prescription opioids (4.1%) and with numbers similar to those of cocaine abuse, comprising approximately 2.2% of the population [61].

Consequently, it is possible to subcategorize BDZ use disorder into two patterns of abuse: deliberate abuse and unintentional abuse [62]. Deliberate abuse happens when
individuals misuse BDZs in order to achieve an altered state of mind due to the drug’s psychoactive effects. Other SUDs often accompany this type of use, and abusers might even take BDZs to self-medicate the withdrawal symptoms of other drugs. On the other hand, unintentional abuse is characterized by a prescribed BDZ medical use that is taken out of its original therapeutical purpose. Those individuals often overuse BDZ by taking a higher dose than necessary due to developed pharmacological tolerance, by using a BDZ drug other than the prescribed one, or might continue taking the medication after the intended treatment to self-medicate episodic anxiety symptoms or even withdrawal symptoms caused by BDZs themselves.

In addition to this, it is fundamental to take into consideration the long-lasting effects that BDZ use disorder might have on brain physiology. When it comes to damage caused by oxidative stress, however, it appears that this pathological process is not present in BDZ use disorder, in both deliberate and unintentional abuse. BDZs bind allosterically to GABAA receptors in several brain areas (Figure 3), potentially reducing excitotoxicity induced by glutamate release and subsequent oxidative damage that arises from this. On the other hand, the pharmacological interactions between BDZs and other drugs are frequent in deliberate abuse and should be taken into consideration when evaluating the extent of the neurotoxic effects of both drugs [63].

It is notably dangerous relationship between BDZ and opioids, especially the unintentional abuse of BDZ in concomitancy with OUD [64], as these drug classes

![Figure 3. Anatomical distribution of the main neurotransmitter systems that BDZs interact with, with special attention to areas related to the symptoms presented in benzodiazepine SUD. Given the pharmacological nature of such drugs, adverse effects on BDZ abuse are mediated almost entirely by GABAergic transmission, mainly in subcortical areas.](Image)

8
are commonly prescribed together. Between 2002 and 2014, the proportion of opioid recipients prescribed concomitantly with a BDZ drug each year had a relative increase of 41% [65], and this pharmacological association is estimated to increase risk of an emergency room visit or inpatient admission for opioid overdose [66].

3. Conclusions

In summary, oxidative stress seems to be involved in alterations in neurochemistry of CNS, neuroinflammatory conditions, and cognitive dysfunctions related to excessive consumption of different depressant drugs, such as benzodiazepines, opioids, and ethanol. Endogenous substances, such as endocannabinoids and exogenous as N-acetylcysteine or phytocannabinoids, have been highlighted as potential drugs/mechanisms of prevention and repair of oxidative stress damage in CNS. Future perspectives include the more selective tests that can point to the mechanisms through which exogenous protective substances act on CNS and interact with endogenous mechanisms of repair on each specific SUD.

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Conflict of interest

The authors declare no conflict of interest.

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Appendices and nomenclature

| ROS       | reactive species of oxygen |
| CNS      | central nervous system    |
| TL4      | toll-like receptor 4      |
| SUD      | substance use disorder    |
| AUD      | alcohol use disorder      |
| OUD      | opioid use disorder       |
| NAC      | N-acetylcysteine          |
| BZD      | benzodiazepine            |
| CBD      | cannabidiol               |
| THC      | Δ9-tetrahydrocannabinol   |
| COX2     | cyclooxygenase 2          |
| IL-1/6   | interleukin 1/6           |
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TNFα  tumor necrosis factor α
GABA  gamma aminobutyric Acid
GSH  glutathione
GSH-Px  glutathione Peroxidase
AMG  amygdala
ACC  anterior Cingulate Cortex
BLA  basolateral Amygdala
CER  cerebellum
HC  hippocampus
NAcc  nucleus accumbens
PFC  prefrontal cortex
SN  substantia nigra
ST  striatum
TH  thalamus
VTA  ventral tegmental area
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