Alcohol and Morphine: Addictive Substances' Impacts on Cell Signaling which Led to Neuroinflammation

Caiyi He[1, †], Ziyang Huang[2, *, †]

[1]University of British Columbia, Canada

[2]South China Normal University, China

[*]20090141060@lfnu.edu.cn

[†]These authors contributed equally

Keywords: Neuroinflammation, Alcohol, Morphine, Opioid, Neuroinflammation, Endotoxin, Central Nervous System

Abstract: Through this paper we will briefly introduce the definition and history of morphine and alcohol. This paper will show the the effect of chronic morphine treatment and alcohol on central nervous system (CNS) which will be analyzed through the opioid signalling pathway and the consequences of the opioid signalling pathways induce that eventually leads to neuroinflammation. Meanwhile, we tried to focus on the differences between these two addictive substances, comparing their pathways and their effect on neuroinflammation.

1. Introduction

There are many medicines and chemicals are originally invented to for sterilize or relieve patients' torment from sickness, surgeries, and/or other symptoms with cautious to the amount should be used from one occasion to the other, but are used in an abusive way to alleviate pressure and find unfeasible happiness, which is completely against its authentic purpose. Eventually, these medicines and chemicals are being called as "addictive substances" is due to reason by which the incautious use of these substances will cause neuropsychiatric disorder that results in consumers forming drug dependencies despite of the damage that these substances may cause [1]. Through scientific studies over the past two decades, scientists have found evidences of the developing patterns that addicts are more likely to develop neuropathies caused by neuroinflammation and their central nervous system (CNS) are severely injured [2,3,4].

When we talk about addictive substances, the largest two categories that usually first come to our minds are drugs and alcohols. Drugs are mostly chemicals extracted from certain plants, they are then purified and maybe crystallized to produce stronger drugs with an exponential growth on the rate of getting addicted to this drug as well as the difficulty to quit. Most of the drugs are not allowed to be sold, some drugs, such as morphine/opiates, are being used under very strict clinical regulations as anesthetics during surgeries to ease patients' pains.

Some neuropathies that have discovered to be largely affected by drug abuse include neurodegenerative diseases such as Alzheimer disease and Parkinson disease; and neuropsychiatric disorders such as depression, autism spectrum disorder, addiction, and Schizophrenia. [2] These neuropathies are all related to different severity of neuroinflammation, which means that addictive substances may have a positive effect in triggering neuroinflammation. Because whenever the press talk about how a new drug is addictive, morphine is being mentioned as a comparison that sometimes it has become a baseline in all drugs. Also, alcohol is being argued about whether it should be sold legally throughout the history due to the fact that many consumers are alcohol addicts who cause many social issues. This paper will mainly focus on discussing the effects of alcohol and morphine, as representative, on cell signaling and the relationship to neuroinflammation.

2. Neuroinflammation

Inflammation is the first immune response to tissue injuries for damage recovering in an expeditious and precise action in order to restore host homeostasis [5]. Numerous cytokines will be released into the brain when neuroinflammation occurs [6]. Microglial cells are brain inflammatory and innate immune cells activated when brain is injured [6,7]. Microglia and other mast cells such as phagocytes are initiated together and will eliminate pathogens in a non-specific manner [5]. They will then stimulate antigen-specific T and B lymphocytes for adaptive immune response, which are then matured into specific types in response of cytokines such as type 1 T helper cells (Th1) and type 2 T helper cells (Th2) [5]. While microglia have two types of activations: classical activation (M1) and alternate activation (M2) [14]. These types of activated microglia that M1 and M2 microglia have pro-inflammatory effects and restore brain damage [6].

Cytokines are produced by neurons and other cells within the immune system and they are composed of small glycoproteins. They are capable of mediating communicative signals between different type of cells during immune response [5]. In general, cytokine include interleukin (IL) family members, such as IL-β and IL-6, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) that are divided into several types and response with different macrophages and lymphocytes [5]. IL-1β is a key immunomodulatory and pro-inflammatory cytokine produced after the formation of inflammasomes [6]. It activates nuclear factor (NF)-kB by stimulating TLR, and then activating chemokines, cytokines, and pro-inflammatory mediator genes [6]. IL-1β can also activate endothelial cells, promote edema and secretion of survival promoting factors by astrocytes, and increase the adhesion of white blood cells [6]. They secrete oxidative metabolites and cytokines (such as TNF, IL-1β, IL-6 and nitric oxide from M1, IL-4, IL-10, and various neurotrophic factors from M2), respectively, to improve damage and prevent inflammation [6].

In cellular immunity, Th1 cytokines and cells are responsible for fight against bacteria, viruses, and autoimmune diseases; Th2 cytokines and cells are involved in humoral immunity to repel extracellular parasites and allergic reactions; there are also pro-inflammatory cytokines that can invade fetal CNS, which are produced by constantly active macrophages and T lymphocytes and mediated by microglia [5]. The activated microglia will also upregulate many receptors' expression in order to increase the producing rate of pro-inflammatory cytokines, which the excessive amount of pro-inflammatory cytokines may cause infections in the circulatory system [5]. Together, microglia and pro-inflammatory cytokines can promote either neuroprotection or neurotoxicity during an inflammatory response [5]. Based on complex signals within the neuronal microenvironment, several pro-inflammatory cytokines, especially TNF-α and IL-6, have both neuroprotective and neurotoxic effects that some pro-inflammatory cytokines have been shown to impede adult neurogenesis in the hippocampus region in a prior investigation [5].

3. Morphine

Morphine, an opioid analgesic, which should be the drug known and used as anesthetic most widely worldwide, is an alkaloid extracted and derived from the opium poppy plant also called *Papaver somniferum* [5]. By law, morphine is a Drug Enforcement Administration (DEA) Schedule II substance which means it has a high potential for abuse and may lead to severe psychological or physical dependence . By history, opium poppy first appeared in ancient record was about 8000 years ago in China, Egypt, Greek, India and Rome and was used by crushing the opioid poppy fruit or dried latex [5]. The actual concept of "morphine" was by a German pharmacist Friedrich Sertürner in 1805 as he was the first scientist published the result of principal psychoactive alkaloid of opium poppy by isolation and purification [9]. With the pure morphine, the usage of each dose became predictable and it could be injected or taken by mouth [9]. The chemical composition of morphine is $C_{17}H_{19}NO_3$ with a systematic name: 7,8-didehydro-4,5-epoxy-17-methyl(5α,6α)-morphinan-3,6-diol.

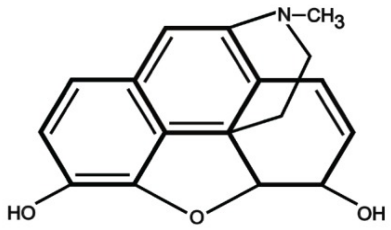

Figure 1. ring structure morphine

The chemical structure of morphine consists of five condensed rings (Fig. 1). The benzene ring (A-ring) and two partially unsaturated cyclohexane rings make up the partially hydrogenated phenanthrene core (B- and C-rings) [10]. It has two hydroxyl function groups (ation [10]).

3.1. Morphine Signaling Pathways

C3 phenolic and C6 alcoholic hydroxyl groups) at positions 3 and 6, as well as an amino group at position 17 [10]. Through long-term usage, morphine will induce neurotoxicity and neuronal dysfunction to the CNS, at the same time, hepatotoxicity, kidney dysfunction, oxidative stress and apoptosis are also induced along with CNS paralyzLike many other drugs, morphine is a highly potent analgesic psychoactive drug acting directly on the CNS to relieve pain meaning the opioid receptors (ORs) are mostly in brains. ORs are a family of seven-transmembrane receptors on cell that are also in the G protein receptor family including δ, μ, κ, and ORL1 (opioid receptor-like 1) receptors [11]. G protein receptors, also known as G-protein-associated receptors (GPCRs), are only found in eukaryotes and comprise of the largest known class of membrane receptors with an important characteristic: they are seven transmembrane α-helices. GPCRs are comprised of three subunits: α-subunit, β-subunit, and γ-subunit. In several receptors, the μ opioid receptor (MOR) is confirmed to be responsible for morphine analgesic signaling. It binds to β-endorphin, an endogenous ligand, to activate several different signaling molecules through Giα subunit [11]. This results in decreasing neuronal excitability as voltage-dependent calcium (Ca2+) channels are inhibited while potassium (K+) channels are promoted [11,12]. MORs are phosphorylated by G-protein-coupled receptor kinases when MORs are activated. Then, arrestins will identify phosphorylated MORs, and clathrin-coated vesicles import them [11]. Next, opioid desensitisation is caused by the brief uncoupling of MORs from signalling pathways caused by phosphorylation and intracellular trafficking of MORs that the majority of internalized MORs resurface on the cell surface, causing resensitization [11]. This is the mechanism of why addicts get high after using drugs, the drugs induce cerebral cortex excitement as ORs can be found on cerebral cortex as well, the switching between sensitization, desensitization, and resensitization that eventually may cause an oxidative environment in brain [10]. When MOR phosphorylation and internalization is not induced effectively, MOR activation will be prolonged that persistent MOR activation on cell surface will alter signal transduction including MOR-coupled G protein Giα change to Gsα, protein kinase C activity level increase, and etc. which will lead to development of morphine tolerance [11]. Adenylyl cyclase (AC), phospholipase C, and etc. are some key enzymes in opioid second messenger concentration modulation [13]. In former studies, the OR activation leads to a severe foremost consequence that second messenger formation is inhibited which results in cyclic adenosine monophosphate (cAMP) reduction, but later studies has shown that cAMP formation is controlled by μ, δ and κ-opioids and cAMP will accumulate in response to μ- and δ-opioids [13]. These are the regular and upstream of the opioid signalling pathway.

3.2. Morphine Mediated Neuroinflammation

The downstream of the opioid signalling pathway are involved and can induce several different damages in different body systems, by which the CNS is being damaged most severely. The opioid induced neuronal damages will then cause neuroinflammation consequently. By definition, neuroinflammation is an inflammatory response occurred in brain towards some brain diseases and/or

neuronal disorders. The most common disease with addicts is hypoxia [10,11,14,11]. Hypoxia is an imbalance within human internal environment resulting an insufficient amount of Oxygen (O_2) circulating in body [10,9,14]. It is very common to find patients who take chronic opioid treatment are having ischemia and hypoxia concurrently. Ischemia a severe disorder forms clots in circulatory system, especially in the cardiovascular and cerebrovascular areas, which will then lead different heart problems and strokes in CNS [14]. Brain under hypoxia for a lengthened time will affect the key inflammatory transcription factors (NF-κB), changes the expression of miRNA, and result in the synthesis and/or release of inflammatory mediators, cytokines and enzymes [14]. Neuroinflammation is regulated by reactive oxygen species (ROS), cytokines and etc. by which ROS and cytokines each plays an important role in neuroinflammation promotion.

As mentioned above, ischemia can induce severe neuroinflammation that through studying ischemia patients, scientists found an increase in protein levels of p53, TP53INP1, and cytokines (TNF-α and IL-1β), and a decrease in miR-125b concentration [14]. During hypoxia or ischemia, δ-opioid receptor (DOR) activation has an influence on miRNA mediated neuroinflammatory response that cells mediated by target genes are affected, when the expression of miR-21, 29a and 29b is regulated after DOR is activated. DOR activation regulates some transcription factors and key molecules, and affects cellular inflammatory response or miRNA biogenesis, leading to neuron survival. DOR activation up-regulates the activity of extracellular signal regulated kinase (ERK), and its signal transduction mediates DOR neuroprotection [14]. The PKCε isoform and Akt pathway are involved in mediating the pro-inflammatory phenotype of mouse microglia induced by morphine [7]. First, morphine can increase LPS-induced PKCε expression and activation, activating the Akt pathway upstream of ERK1 / 2 and iNOS [7]. Activation of the Akt pathway is closely associated with activation of PKCε in the cell line. Second, PKCε can selectively inhibit and regulate μ-opioid receptor signaling on microglia and diminish glial cell activation [7]. By acting on the Akt-ERK1 / 2 signaling pathway via the μ-opioid receptor, morphine activates microglia to produce NO^- and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) releases [7]. Glial and morphine opioid receptors allow microglia to increase their ability to produce pro-inflammatory cytokines, resulting in direct interaction between morphine and glial cells. PKCε affects morphine-induced inflammatory pathways that can lead to the production of chemokines and NO^- [7]. These signaling pathways mediate the pro-inflammatory phenotype of mouse microglia in response to morphine treatment. By RNA interference and pharmacological inhibitors, morphine-induced IL-1β, iNOS, IL-6, TNF-α, and NO production in microglia is mediated by a signaling pathway with continuous activation of PKCε and Akt and caused by MAPK [7]. Eventually, neuroinflammation occurs in brain.

3.2.1. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)

In a pathological view, ROS are important factors in enhancing aging and with the imbalance/excessive amount of ROS, many pathologies such as endoplasmic reticulum (ER) stress induced neuroinflammation and cardio problems are promoted [10,15]. But in a biological view, ROS mediate cell growth, apoptosis, some cellular signalling, and other complex functions such as blood pressure regulation and immune function [15]. Like ROS, reactive nitrogen species (RNS) have many different functions that can be either beneficial or harmful to the body system. Some RNS are important physiological process regulators that by reacting with other oxidants, they can regulate cellular toxicity damages towards metabolic enzymes and the generation of metabolic enzymes [15]. ROS include hydroxyl radical ($^{\bullet}OH$) and superoxide ($O_2^{\bullet -}$), and hydrogen peroxide (H_2O_2) [10,15]. RNS include nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), hypochlorous acid (HOCl), and peroxynitrite ($ONOO^-$) [10,15]. H_2O_2, HOCL, and $ONOO^-$ are non-radical species while all others are radical species, which means they are highly reactive [15]. Although $ONOO^-$ is non-radical species, but it is a powerful oxidant that is capable of causing damages to many different organic molecules [15]. Our body has both oxidative system and antioxidative system. Under normal condition, the amount of antioxidants are efficient to neutralize maternal oxidants to maintain the redox homeostasis [10]. Sustained morphine treatment will tip the balance between the two systems resulting disproportional amount of oxidants being produced that there are more numbers of oxidants

than the number by which antioxidants can neutralize, therefore hypoxia, an oxidative environment, is caused inside brain area and other organelles [15]. The most significant enzymes involved in oxidant neutralization are superoxide dismutase (SOD), glutathione-peroxidase (GSHPx) and catalase (CAT), but tripeptide glutathione (GSH) is also a key molecule involved in this process [10]. Through experiments, it has been indicated that chronic morphine treatment decreases the activeness of these enzymes and molecule that they do not neutralize oxidants anymore and hypoxia is induced into CNS along with a promotion in cytokines production [10].

4. Alcohol

Alcohol, also known as Ethanol, is a main alcohol made composed of ethane with a hydroxy group in place of one of the hydrogens. It functions as an antiseptic, polar solvent, neurotoxic, central nervous system depressant, teratogenic agent, NMDA receptor antagonist, protein kinase C agonist, disinfectant, human metabolite, Saccharomyces cerevisiae metabolite, Escherichia coli metabolite, and mouse metabolite. It's an alkyl alcohol, a volatile organic chemical, and a part of the ethanol family. It's an ethoxide's conjugate acid.

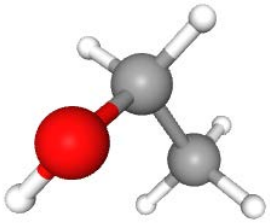

Figure 2. Structure of alcohol

In the field of human research, Alcohol is a depressant of the central nervous system (CNS). It improves the inhibitory effects of γ-aminobutyric acid (GABA) at the GABA-A receptor and inhibits glycine binding at the N-methyl-d-aspartate receptor in a competitive manner (it disrupts excitatory glutaminergic neurotransmission). Other inhibitory neurotransmitters, including as dopamine and serotonin, are similarly stimulated by ethanol. Ataxia, lethargy, vomiting, and recumbency are the most typical symptoms of ethanol poisoning.

4.1. Alcohol Signaling Pathways

Ethanol is a psychoactive stimulant with rewarding and sedative-hypnotic qualities. Its acute actions on certain signaling proteins cause changes in location, post-translational modifications, gene expression, and neuronal excitability.[16] There are a lot of pathways included

4.1.1. cAMP-Dependent Protein Kinase A(PKA)

PKA is involved in memory and learning, as well as behavioral reactions to drugs of abuse. It occurs as a tetramer with two regulatory and two catalytic subunits that is inactive.Activation of adenylyl cyclase (AC) catalyzes the conversion of ATP to cyclic adenosine 3′, 5′-monophosphate (cAMP). PKA is activated by cAMP binding to regulatory subunits, which causes them to dissociate from catalytic subunits, allowing them to become active.

Ethanol, like other addictive substances, raises extracellular dopamine levels in the nucleus accumbens (NAc)[17], activating D1 dopamine receptors connected to Gs and Golf, as well as AC and PKA.Ethanol promotes AC/PKA/DARPP-32 signaling in a variety of ways. Ethanol raises extracellular dopamine levels in the NAc.

Ethanol promotes AC/PKA/DARPP-32 signaling in a variety of ways. Ethanol raises extracellular dopamine levels in the NAc through boosting dopamine neuron activity in the ventral tegmental area (VTA)[17]. Low concentrations of ethanol, as well as other addictive substances like opiates,

cannabis, and nicotine, can operate synergistically to stimulate ACs by combining actions at A2a receptors, which activate Golf, and dopamine D2 receptors, which trigger Gβγ subunit release [18].

4.1.2. Protein Kinases C (PKC)

The activation of type 1 corticotrophin releasing factor (CRF) receptors is required for ethanol to promote GABA release in the CeA. (CRF1Rs). CRF is an anxiogenic neuropeptide that promotes excessive ethanol consumption by acting on CRF1Rs in the amygdala of ethanol-dependent animals.[19]

4.2. Alcohol Mediated Neuroinflammation

Chronic alcohol use has been linked to neuroinflammation, neuronal damage, and behavioral changes, including addiction. Increased production of proinflammatory cytokines (such as TNF, IL-1, and CCL2), as well as microglial activation, define alcohol-induced neuroinflammation. Research showed that Microglia activation and peripheral macrophage infiltration were seen in the CNS, notably in the hippocampus, after chronic alcohol use.Dual CCR2/5 inhibitor cenicriviroc (CVC) treatment prevented ethanol-induced peripheral macrophage recruitment and partially reversed microglia activation. Chronic alcohol intake also increased the expression of proinflammatory markers in multiple brain areas, including the cortex, hippocampus, and cerebellum. Alcohol-mediated production of inflammatory markers was reduced when CCR2/5 was inhibited.[20]

There's a growing amount of data showing there's a relationship between alcohol and inflammation in the brain. TLRs modulate the effects of alcohol intoxication, withdrawal, and chronic use on the immune system, triggering microglial activation and the release of pro-inflammatory cytokines. Alcohol has an effect on the peripheral immune system as well, producing thiamine deficiency as well as an increase in A precursors in the brain.

TLR2/4 stimulation is caused directly by alcohol, and when combined with fAβ, it results in enhanced microglial activation and increased inflammatory cytokines and chemokine release. Indirectly, alcohol induces elevated circulation cytokines, including TNFα, IL-1β, IL-6, and endothelial production of prostaglandins and iNOS, which promote direct microglial cell activation and contribute to neuroinflammation through cytokines and chemokines release. Due to a combination of elevated inflammatory mediators and diminished or saturated microglial cells, the aggregate of impacts leads in more neurodegeneration and cell death, more microglial burn-out, and increased Aβ aggregation.[21]

5. Conclusions

As the two of the most famous addictive Substances, morphine and alcohol have been studied quite a lot, the differences between their mechanism is interesting and of academic value.

On one hand, for decades, scientists have been studying drugs and analgesics, but due to the fact that normal civilians cannot control their selves from over using these analgesic drugs, strict laws have come out that there are actually few studies and experiments down in this field when comparing to other fields such as plant physiology and etc. Comparing opioid/morphine to other drugs, its journals of studies are relatively easier to find. However, the research directions of each opioid paper is quite different, it became very hard to conclude the mechanisms together and sometimes the theories of the mechanisms of a part of the opioid signalling pathway conflicts with each another that it was very hard at some points to decide which information should be used in the paper.

On the other hand, alcohol has been widely recognized as a killer of mankind. Many researches have shown that it plays an essential part in metabolism. For example, a variety of neurological illnesses such as stroke, brain tumors, multiple sclerosis (MS), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) have been proved related to overdose of alcohol as the central nervous system (CNS) is the primary target of alcohol's negative effects[22].

We hope that our review will provide a more detailed and most up-to-date information in the morphine and alcohol induced neuroinflammation study to help alert some addicts to consider quit

taking drugs or quit drinking. But the actual meaning of this review is to encourage more future scientists to ponder about devoting their specialized knowledge in a field that is very close to our everyday life as there are many possibilities to be found in this field such as Merighi et al. mentioned in their paper that DOR is capable of suppressing some pro-inflammatory cytokines' expressions. With more and more research, we believe more application with analgesics' extractions can be found, and lives of mankind can be improved.

References

[1] Zou Zhiling, Wang Huijun, Uquillas Federico d'Oleire, Wang Xiaomei, Dingn Jianrui, Chen Hong. Definition of Substance and Non-substance Addiction [J]. Advances in Experimental Medicine and Biology, 2017, 1010: 21-41

[2] Hong Heeok, Kim Byung Sun, Im Heh-In. Pathological Role of Neuroinflammation in Neurodegenerative Diseases and Psychiatric Disorders [J]. International Neurourology Journal, 2016, 20(Suppl 1): S2-S7

[3] Fitting Sylvia, Zou Shiping, El-Hage Nazira, Suzuki Masami, Paris Jason J., Schier Christina J., Rodriguez Jose W., Rodriguez Myosotys, Knapp Pamela E., Hauser Kurt F.. Opiate Addiction Therapies and HIV-1 Tat: Interactive Effects, on Glial [Ca2+]I, Oxyradical and Neuroinflammatory Chemokine Production and Correlative Neurotoxicity [J]. Current HIV Research, 2014, 12(6): 424-434.

[4] Krasnova Irina N., Justinova Zuzana, Cadet Jean Lud. Methamphetamine addiction: involvement of CREB and neuroinflammatory signaling pathways [R]. Psychopharmacology (Berl), 2016, 233(10): 1945-1962

[5] Na Kyoung-Sae, Jung Han-Yong, Kim Yong-Ku. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia [J]. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2014, 48: 277-286

[6] Liu Rui, Pan Meng-Xian, Tang Jun-Chun, Zhang Hua-Bao, Zhuang Yang, Zhao Dan, Wan Qi. Role of neuroinflammation in ischemic stroke [J]. Neuroimmunol Neuroinflammation, 2017, 4: 158-166

[7] Merighi Stefania, Gessi Stefania, Varani Katia, Fazzi Debora, Stefanelli Angela, Borea Pier Andrea. Morphine mediates a proinflammatory phenotype via μ-opioid receptor-PKCε-Akt-ERK1/2 signaling pathway in activated microglial cells [J]. Biochemical Pharmacology, 2013, 86(4): 487-496

[8] Brook Karolina, Bennett Jessica, Desai Sukumar P.. The Chemical History of Morphine: An 8000-year Journey, from Resin to de-nove Synthesis [J]. Journal of Anesthesia History, 2017, 3(2): 50-55

[9] Tomohiko Aoe. Development of Opioid Tolerance and Endoplasmic Reticulum Stress [R]. Journal of Pain & Relief, 2015, 4(2): 1-4

[10] Sil Susmita, Palsamy Periyasamy, Guo Ming-Lei, Callen Shannon & Buch Shilpa. Morphine-Mediated Brain Region-Specific Astrocytosis Involves the ER Stress-Autophagy Axis [J]. Mol Neurobiol, 2018, 55: 6173-6733

[11] Gintzler Alan R. and Chakrabarti Sumita. Opioid Tolerance and the Emergence of New Opioid Receptor-Coupled Signaling [J]. Molecular Neurobiology, 2000, 21: 21-33

[12] Chen Yi-Meng, He Xiao-Zhou, Wang Shu-Ming and Xia Ying. δ-Opioid Receptors, microRNAs, and Neuroinflammation in Cerebral Ischemia/Hypoxia [R]. Frontiers in Immunology, 2020, 11(21): 1-11

[13] Courtwright David T.. Forces of Habit: Drugs and the Making of the Modern World [Book]. Harvard University Press, 2001, (1): 36-38

[14] Skrabalova Jitka, Drastichova Zdenka, and Novotony Jiri. Morphine as a Potential Oxidative Stress-Causing Agent [J]. Mini-Reviews in Organic Chemistry, 2013, 10(4): 367-372

[15] Meo Sergio Di, Reed Taenea T., Venditti Paola, and Victor Victor Manuel. Role of ROS and RNS Source in Physiological and Pathological Conditions [J]. Oxidative Medicine and Cellular Longevity, 2016, 2016: 1245049

[16] Ron D, Messing RO. Signaling pathways mediating alcohol effects. Curr Top Behav Neurosci. 2013; 13:87-126.

[17] Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A. 1988;85(14):5274–5278.

[18] Yao L, Fan P, Jiang Z, Mailliard WS, Gordon AS, Diamond I. Addicting drugs utilize a synergistic molecular mechanism in common requiring adenosine and Gi-beta gamma dimers. Proc Natl Acad Sci U S A. 2003;100(24):14379–14384.

[19] Chu K, Koob GF, Cole M, Zorrilla EP, Roberts AJ. Dependence-induced increases in ethanol self-administration in mice are blocked by the CRF1 receptor antagonist antalarmin and by CRF1 receptor knockout. Pharmacol Biochem Behav. 2007;86(4):813–821.

[20] Lowe PP, Morel C, Ambade A, Iracheta-Vellve A, Kwiatkowski E, Satishchandran A, Furi I, Cho Y, Gyongyosi B, Catalano D, Lefebvre E, Fischer L, Seyedkazemi S, Schafer DP, Szabo G. Chronic alcohol-induced neuroinflammation involves CCR2/5-dependent peripheral macrophage infiltration and microglia alterations. J Neuroinflammation. 2020 Oct 9;17(1):296.

[21] Venkataraman A, Kalk N, Sewell G, Ritchie CW, Lingford-Hughes A. Alcohol and Alzheimer's Disease-Does Alcohol Dependence Contribute to Beta-Amyloid Deposition, Neuroinflammation and Neurodegeneration in Alzheimer's Disease? Alcohol Alcohol. 2017 Mar 9;52(2):151-158.

[22] Pervin Z, Stephen JM. Effect of alcohol on the central nervous system to develop neurological disorder: pathophysiological and lifestyle modulation can be potential therapeutic options for alcohol-induced neurotoxication. AIMS Neurosci. 2021 Apr 9;8(3):390-413.