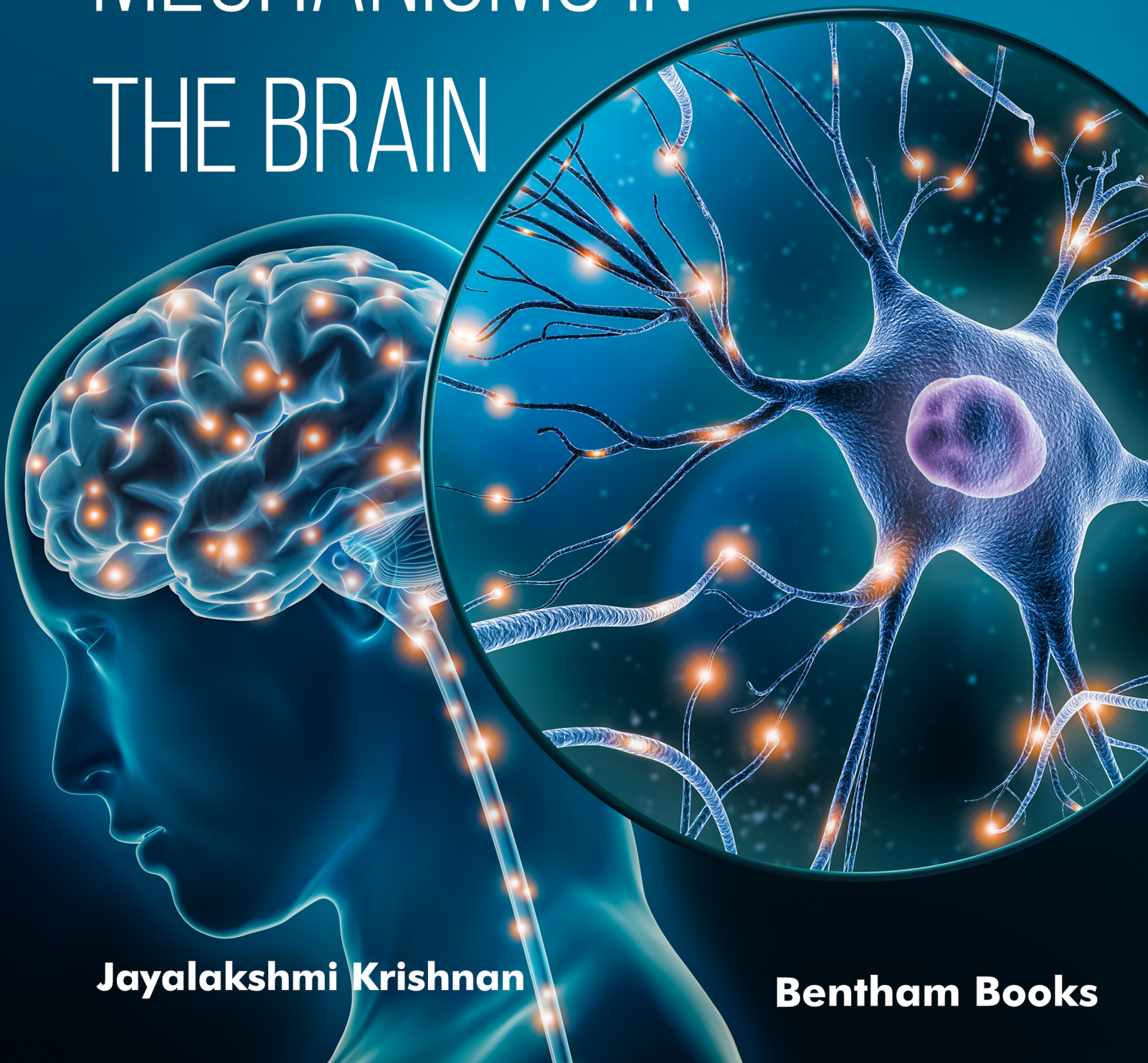
DRUG ADDICTION MECHANISMS IN THE BRAIN



Jayalakshmi Krishnan

Bentham Books

Drug Addiction Mechanisms in the Brain

Authored by

Jayalakshmi Krishnan

Department of Life Sciences
Central University of Tamil Nadu
Tamil Nadu
Thiruarvur, India

Drug Addiction Mechanisms in the Brain

Author: Jayalakshmi Krishnan

ISBN (Online): 978-981-5223-82-8

ISBN (Print): 978-981-5223-83-5

ISBN (Paperback): 978-981-5223-84-2

First published in 2024.

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

It is generally believed that drug abuse can cause severe long-lasting changes in the neural network contributing to the development of addiction. Profound states of addiction may be established in brains with repetitive usage, despite its damage to the brain. Dopamine plays a very significant role in addiction to drugs. Under normal conditions, in neural communication between neurons, the presynaptic neuron releases dopamine into the synapse. At the postsynaptic neurons, there are receptors which receive the dopamine. Usually, any left-out dopamine molecule is recycled back to the presynaptic neuron by the dopamine transporters. If any drug blocks the dopamine transporter it is unable to take the dopamine back from the synaptic cleft leading to the continuous firing of neurons. As per Drug Enforcement Administration (DEA) and the Controlled Substances Act (CSA) reports, heroin is a Schedule I drug. Heroin causes addiction to the brain like any other addictive substance. Heroine use affects not only neurotransmitters but also the hormonal systems in an irreversible way. In healthy young people, the use of MDMA can lead to cognitive decline when abused with cannabis. MDMA causes hyponatremia and hyponatremia-associated deaths. This book deals with the harmful effects of drugs on brain and cognitive functions. I wish our readers can be satisfied with many questions and feel excited to find the answer to the research questions on the etiology of neurological sequelae of drug abuse in this book.

Jayalakshmi Krishnan
Department of Life Sciences
Central University of Tamil Nadu
Tamil Nadu
Thiruarvur, India

CHAPTER 1

Cocaine and its Effects on the Brain

Abstract: Brain's limbic system is the target site of action of cocaine. This area of the brain is involved in pleasure and motivation. Cocaine causes the dopamine build-up in the synapses by creating a feeling of being "high". Cocaine induces action by binding to the dopamine transporter, which transports excess dopamine back to the presynaptic neuron. The nucleus accumbens (NAc) of the limbic system is the primary target of cocaine action. Cocaine also alters gene expression in the limbic system by altering dopamine transporters or dopamine receptors. Cocaine causes auditory hallucinations, restlessness, paranoia, and psychosis. This chapter reviews the impact of cocaine on the brain.

Keywords: Cocaine, Limbic system, Nucleus accumbens (NAc).

INTRODUCTION

It is generally believed that drugs of abuse can cause severe long-lasting changes in the neural network contributing to the development of addiction. Cocaine is the most powerful reinforcing drug of abuse which can bind to serotonin transporter (SERT), dopamine transporter (DAT), and norepinephrine transporter (NET) by causing blocking of the reuptake of these neurotransmitters. Cocaine is a CNS stimulant that alters sleep and causes alertness. Withdrawal of cocaine is always accompanied by lack of motivation, increased irritability, agitation, extreme fatigue, and depression. Anxiety is one of the main symptoms of cocaine withdrawal and corticotropin releasing factor/hormone (CRF or CRH) has been involved in cocaine abstinence.

Cocaine is synthesized from the coca plant, a native of South America. It is sold as a solid rock crystal form or a fine white powder. Cocaine can be snorted, rubbed in water in the gums, and can be injected with a needle. Another method of taking cocaine is just heating up the rock crystal and directly inhale.

Profound states of addiction to cocaine may be established in brains with repetitive usage, despite its damage to the brain. Studies in animal models prove that the limbic system, basal ganglia, and ventral striatum are involved in dopaminergic neurons that cause pleasure experience [1 - 3]. Continuous use of

Jayalakshmi Krishnan

cocaine can lead to damage to the structural components of the brain, causing mental health disorders such as anxiety and depression and loss of gray matter in the brain, followed by the death of neuronal cells. Cocaine also damages breathing, the immune system, heart dysfunctions, and digestive system problems. Cocaine alters the signalling of neurotransmitters in the brain. Information processing and emotions are affected by cocaine addiction, and also the prefrontal cortex becomes sensitive to cocaine addiction. Although some of the effects of cocaine on the brain are known, many things remain unknown, especially the chronic changes associated with cocaine exposure. Cocaine exposure also alters the learning process within the striatum and prefrontal cortex according to some animal studies. Low doses of cocaine can be dangerous. A single low dose of cocaine can cause structural brain damage in Balb-c mice (o.5mg/kg) without altering the metabolism [4]. As per the European drug report, 4.3 million people between 15 and 64 years old have used cocaine (European Drug Report, 2016). Cocaine also causes myocardial infarction and psychiatric illness [5].

In vitro and *in vivo* experiments have shown a different kind of trend when cocaine is administered. Cocaine causes less firing in neurons *in vivo*, whereas deep hyperpolarization *in vitro.* Withdrawal of cocaine leads to the impairment of sodium currents in nucleus Accumbens neurons [6]. Not only sodium currents but calcium homeostasis is also affected by cocaine in the nucleus Accumbens neurons [7]. Calcineurin is a calmodulin-dependent serine/threonine protein phosphate whose levels were decreased in neurons due to cocaine uptake (Hu *et al.*, 2005). Whole cell calcium levels are affected due to chronic cocaine intake and distups, synaptic plasticity, and intracellular signaling cascades with substantial changes in neurotransmitter release [8].

Cocaine in Brain

Under normal conditions, in neural communication between neurons, the presynaptic neuron releases dopamine into the synapse. In the postsynaptic neurons, there are receptors that receive this dopamine. Usually, any left-out dopamine molecule is recycled back to the presynaptic neuron by the dopamine transporters. Cocaine intake binds with the dopamine transporter and blocks the normal recycling process. This results in the build up of dopamine in the synapses, contributing to the pleasurable effects of cocaine. Cocaine is also a psychostimulant [9]. In brain, cocaine usage can create a short-term change such as alertness, feeling of pleasure, increased energy, overactive, paranoia, *etc.* Significant neurological adaptation can be seen in mice after cocaine exposure in terms of the release of the excitatory neurotransmitter glutamate [10]. Cocaine use is also related to stress and both co-occur at any time [11]. Stress pathway and reward pathway are different in brain, but both can overlap by connections from

the ventral tegmental area. Functioning of the orbitofrontal cortex (OFC) is also reduced due to chronic cocaine exposure leading to poor decision making [12]. Ventral pallidum (VP) is connected to the nucleus Accumbens *via* both direct and indirect pathways. Cocaine reinforcement is mediated through Ventral pallidum (VP), which is a part of the basal ganglia. Cocaine inhibits the indirect pathway of neuronal synaptic transmission in VP [13]. By inhibiting the reuptake of 5-HT, cocaine increases extracellular concentrations of serotonin (5-hydroxytryptamine or 5-HT) in the nucleus accumbens [NAc] and ventral pallidum. Cocaine also disturbs the learning and memory pathways of brain. Long-term potentiation is affected due to cocaine administration. Transcription factor ΔFosB in longterm cocaine administration, causes NMDR activation in NAC [14]. ΔFosB concentrations are increased in reinforcing effects of cocaine.

Effects of Cocaine on Brain Cells

Cocaine releases CXCL10 from pericytes and it regulates monocyte transmigration into the CNS [15]. Cerebrovascular accidents are the most common form of cocaine abuse [16]. The neurotoxicity of cocaine addiction is also due to oxidative stress, autooxidation, and apoptosis [17, 18]. Continuous exposure to a psychostimulant drug can lead to changes in cerebral glucose metabolosim [19, 20]. Cocaine causes autophagic cytotoxicity by activating the nitric oxide GAPDh signaling cascade [21]. Mesocorticolimbic dopamine system is the main reason for cocaine seeking behaviour when activated [22]. Cocaine and methamphetamine users experience changes in the orbitofrontal cortex. OFC and medial prefrontal cortex (mPFC) in rats, when analysed for spine density, revealed a profound change [23]. Alertness, attention, and energy are elevated in cocaine users.. In hippocampal neurons and astrocytes glial fibrillary acidic protein is expressed in response to cocaine administration [24]. When BV2 microglial cells were exposed to cocaine, it altered exosome biogenesis [25].

Cocaine at the Synapse

Cocaine affects DA levels in the mesolimbic reward pathway. Cocaine binds to the dopamine transporter (DAT), hence blocking the reuptake of dopamine in the presynaptic terminal. Because of this, the extracellular dopamine level is increased by much magnitude. DAT is a protein located in the presynaptic neuron, and the functioning of DAT is essential for proper dopamine neurotransmission [26].

Cocaine can also increase all monoamine neurotransmitter levels in the brain, not only dopamine. Serotonin and norepinephrine levels are also increased by cocaine use. The reinforcing effects of cocaine are due to the dopamine levels. Cocaine also alters NMDA dependent signal transduction in straital neurons. Repeated

CHAPTER 2

Heroin and its Effects on the Brain

Abstract: As per the Drug Enforcement Administration (DEA) and the Controlled Substances Act (CSA) reports, heroin is a Schedule I drug. Heroin causes addiction to the brain like any other addictive substance. Heroin addiction has both long-term and short-term effects on the body. The brain has natural opioid receptors. Heroin is a synthetic opioid. When taken regularly, the brain stops making its own natural opioids. This affects the pain/reward system and causes withdrawal symptoms in patients. Heroin addiction damages the brain's reward system and breathing. Less breathing causes less oxygen supply to the brain. There are reports that state that dementia-like situation is created in the brain due to heroin abuse. Heroin lipophilicity allows the entry of it into the Blood Brain Barrier. μ-opioid receptors (MOR), causing the addictive effects of the heroin in the brain. Dementia symptoms, memory issues, and mental health changes like depression or anxiety are the symptoms that are caused by heroin abuse. Both individual and environmental factors influence a person's ability to abuse heroinanopioid which provides intense feelings of pleasure.

Keywords: Anxiety, Dementia symptoms, Depression, Heroin, Memory issues, Opioid, μ-opioid receptor (MOR).

INTRODUCTION

Heroin use affects not only neurotransmitters but also the hormonal systems in an irreversible way [1, 2]. Human studies have shown white matter deterioration in heroin users [3, 4]. Physical dependence and tolerance are the two effects of heroin use. Withdrawal of the drug is caused within hours of the last drug ingestion characterised by muscle and bone pain, vomiting, insomnia, diarrhoea, restlessness, and cold flashes. Heroin use disorder is caused by repeated heroin use and it is accompanied by uncontrolled drug seeking. Needle sharing and injection is the main cause of HIV in patients with heroin use. The other dangerous effect of using Heroin in pregnant mothers is that it crosses the placenta and it makes the baby in the womb to be dependent on the drug called neonatal abstinence syndrome (NAS). Overdose of heroin can be dangerous to the life-threatening cause and requires medical attention. Almost 75% of heroin users are identified with mental health issues such as Borderline personality disorder, ADHD, depression, or bipolar disorder [5 - 7]. Many people with substance use disorder may have mental health issues or *vice versa*. Research also points out

that co-occurring mental illnesses are common in adolescents with substance use disorders. Generalized anxiety disorder, panic disorder, and posttraumatic stress disorder are widespread in co-morbid substance use disorder. Heroin is classified as Schedule I drug as per the regulations of the Drug Enforcement Administration and Controlled Substances Act. After taking heroin immediately, the users feel high pleasure. Between 4 to 5 hrs, this effect is seen. Based on the methods of administration, this effect can be seen. For example, it can be seen within 20 seconds, peaking after 2 hours and up to 4 hours. Heroin is a very addictive opioid that decreases pain, induces euphoria and warmth, and causes drowsiness. Naloxone is the medicine which is used to treat heroin overdose. From 2007, the use of heroins among people is increasing. Medication-assisted treatment (MAT) is the treatment for heroin addiction. Methadone and buprenorphine can help withdrawal symptoms. Smoking or snorting can cause the high within about 10 minutes and can persist 4 to 5 hours.

Heroin and the Brain

Pain perception mechanisms are modulated by heroin use. Heroin belongs to illicit opioid drugs that can become morphine-like substances when entered into the brain. Heroin, upon entry into the brain, binds to opioid receptors in the brain stem, and the body. This heroin opioid inhibits gamma-aminobutyric acid (GABA), upon doing it, the level of dopamine is increased in brain. The reinforcing property of heroin is due to the secretion of Dopamine at excess levels. Responding to stressful stimuli, managing behaviour, and decision-making is affected by heroin use due to white matter decay [8]. The basal ganglia, prefrontal cortex, extended amygdala are the regions affected by drug abuse. Reward circuit in the basal ganglia is over activated by drugs causing euphoria of the drug high. The basal ganglia play an important role in positive forms of motivation. Repeated exposure to a drug causes this pathway to be adapted to the drug, reducing the sensitivity to the need for more doses of the drug to get the same feeling. Anxiety, irritability, and unease are stress feelings which are caused by withdrawal of the drug Opioid can cause death if taken overdose as it causes decreased breathing. These effects are due to the changes in brain stem which controls heart rate, breathing, and sleeping. Overdose of heroin causes hypoxia that leads to short-term and long-term effects on neuronal cells. Repeated heroin use causes heroin use disorder leading to uncontrolled drug seeking.

Heroin is extremely addictive; withdrawal begins within 5 hours.

Action of Heroin on Mu-opioid Receptors

Mu-opioid receptors (MoRs) are considered the reward system of the brain. When dopamine binds to these receptors, it creates a sense of well-being or pleasure.

Heroin binds to these receptors, thus mimicking the effect of dopamine. Heroin also damages the white matter, thus, in turn, affecting people's decision-making ability, self-control, and ability to face difficult situations in life. Structural changes are also noticed in the brain due to heroin usage such as depression, paranoia, and psychosis. Venus sclerosis is also one of the effects of the usage of heroins, thus affecting venous circulation. An unnatural sense of well-being is one of the short-term effect of heroin usage.

Mental confusion and difficulty in thinking were also noticed as short-term changes in heroin usage. Unnatural mood swings, depression, insomnia, paranoia, psychosis are the long-term effects of heroin usage. Upon entry into the brain, heroin is converted as morphine. Not only heroins but prescription drugs such as OxyContin (oxycodone), Vicodin (acetaminophen/hydrocodone), fentanyl, methadone, and Dilaudid (hydromorphone) can gel with opioid receptors and cause the release of dopamine.

There was a study on the brains of postpartum samples of victims who died of heroin abuse. Their brains have shown tremendous changes in the neurogensis process. Such changes are noted by changes in reduced neural progenitor cell number, cell proliferation rates were low, and there was also less number of dendritic trees [9]. Cynomolgus macaques have shown a different gene expression pattern in response to heroin administration in the hippocampus and striatum at different points of their age. Upon treatment with heroin, the animals have shown differential expression in genes related to dopamine, synapse, autophagy, and neurotrophin signalling [10, 11].

CONCLUSION

Heroin use disorder is caused by repeated heroin use and it is accompanied by uncontrolled drug seeking. Needle sharing and injection is the main cause of HIV in patients with heroin use. The other dangerous effect of using Heroin in pregnant mothers is that it crosses the placenta and makes the baby in the womb dependent on the drug called neonatal abstinence syndrome (NAS). Overdose of heroin can be dangerous to the life-threatening cause and requires medical attention. Pain perception mechanisms are modulated by heroin use. Heroin belongs to illicit opioid drugs that can become morphine-like substances when entered into the brain. Heroin, upon entry into the brain, binds to opioid receptors in the brain stem, and the body. This heroin opioid inhibits gamma-aminobutyric acid (GABA); upon doing it, the level of dopamine is increased in the brain. Mental confusion and difficulty in thinking were also noticed as short-term changes in heroin usage. Unnatural mood swings, depression, insomnia, paranoia,

CHAPTER 3

MDMA (3,4-methylenedioxy-methamphetamine)

Abstract: 3,4-methylenedioxy-methamphetamine (MDMA) is a synthetic drug very similar to hallucinogens and stimulants. This drug is also called ecstasy or molly. It produces feelings of pleasure, warmth, distorted sensory time and perception. MDMA increases the activity of serotonin, dopamine and norepinephrine in the brain. It causes various health effects such as nausea, sweating, chills, muscle cramping, *etc.* The effect of this drug can be seen in 3 to 5 hours in the body. A spike in body temperature can be seen in MDMA users that can be fatal as it affects the liver, kidney, and heart leading to death. Addiction to MDMA is not yet proven, however, withdrawal symptoms such as fatigue and depression are noted. MDMA is usually taken *via* the mouth or snorting in the form of tablets or capsules. This drug is also taken or abused along with other drugs such as LSD, alcohol, and marijuana. MDMA is a scheduled drug with no proven medical use. MDMA causes a surge of serotonin, dopamine, and norepinephrine in the brain to regulate mood, learning, memory, stress, anxiety, *etc.* This chapter discusses the effects of MDMA on the human brain.

Keywords: Dopamine, Memory, MDMA on the human brain, Norepinephrine learning.

INTRODUCTION

In healthy young people, the use of MDMA can lead to cognitive decline when abused with cannabis. Impairment of working memory is considered a cognitive decline parameter [1]. Plasma membrane serotonin transporter (SERT), is reduced in heavy MDMA users [2]. Dose-dependent reductions in 5-HT were seen in all brain regions of rats upon MDMA administration. Norepinephrine and/or dopamine levels are also reduced in some of the brain regions. In the guinea pig brain 20mg/kg dose of MDMA reduced 5-HT in all brain regions [3]. In MDMA-treated monkeys, even after 7 years, abnormal brain 5-HT innervation patterns were seen [4]. Losses of serotonergic (5-HT) axons are seen throughout the forebrain during 20 mg/kg, s.c., twice daily for 4 d in rat brain. Logohhera psychomotor drive and enhanced insight are noted in subjects along with toxic psychosis [5]. METH and cocaine are classified as stimulants, however, there are key differences between them. The key differences include drug type, classification and origination, process of metabolization/half-life, appearance, and

Jayalakshmi Krishnan

effects on the brain and body. METH is a man-made synthetic chemical; however, cocaine is synthesised from the coca plant. These two drugs also differ in their half-life, for cocaine, the half-life is one hour but for METH half-life is 12 hours. Coke appears as a fine white powder, whereas METH is appear like crystal glass powder. Both drugs block the reuptake of dopamine in the brain, however, METH also increases the release of dopamine in the brain contributing to more dopamine levels. The addictive potential of METH is less understood than other drugs.

Norepinephrine (NE) and MDMA

Norepinephrine (NE) transporter inhibitor reboxetine has been observed to reduce the BP heart rate and high feeling. NE levels, stimulation, and excitation in healthy subjects [6]. MDMA causes hyponatremia and hyponatremia-associated deaths [7]. Tryptophan hydroxylase is released due to oxidative stress due to MDMA, leaving the cell vulnerable to oxidative stress. MDMA also releases norepinephrine, dopamine, and acetylcholine release and acts on various receptors such as alpha 2-adrenergic and 5-hydroxytryptamine (5-HT) 2A receptors. Receptors such as 5-HT2 and 5-HT1 are known to play a role in MDMA responses. Among these receptors, 5-HT2 receptors mediate positive mood but not negative mood [8]. MDMA is proven to act through serotonin receptor binding with high affinity [9].

In squirrel monkeys, which is a human primates, it is shown that a single oral dose of MDMA (5.7 mg/kg) has created long-lasting serotonergic defects [10]. Radioligand carbon-11-labeled McN-5652 in the human brain under PET study has shown that 5 HT binding was decreased [10]. In MDMA users, 5-HT transporter (SERT) reduced binding in multiple brain regions and DAT binding [11]. Cerebral presynaptic serotonergic transmitter system was changed in human young adults as revealed by a positron emission tomography study [12].

Ketanserin,5-HT2 receptor antagonist, has been shown to decrease the effect of MDMA on emotional excitation and perception [13]. Doxazosin, an α_1-noradrenergic receptor antagonist, was shown to be cardiogeneic and thermogenic, contributing to the euphoric effects of MDMA in humans [14]. The stimulant effect of MDMA is reduced by reboxetine, a norepinephrine transporter inhibitor. Moreover, MDMA plays a role in increasing or decreasing the body temperature and MDMA is an alpha-adrenoceptor agonist like clonidine which produces hypothermia [15]. Plasma oxytocin levels were increased to a peak of 83.7 pg/ml after MDMA (1.5 mg/kg) at 90-120min time in healthy volunteers with MDMA use [16]. Emotional empathy was noticed in MDMA doses without affecting cognitive empathy [17].

Antioxidant and Signalling Pathways and MDMA

The brain's antioxidant system is also affected due to MDMA treatment. For example, in male rats after MDMA treatment, superoxide dismutase levels (SOD1) were increased in the female brain whereas SOD2 was increased in the male brain. It is also found that the male brain is very sensitive to the effects of MDMA-induced neurotoxic effects [18]. In rat cortical neurons treated with MDMA, it was found that under the influence of MDMA, the autophagy process is ii dated with the activation of AMPK/ULK1 signaling pathway [19]. MDMA also triggers autophagy in serotonergic neurons in cultured rat neurons [20 - 22]. Behavioural sensitization in C57BL/6J mice is due to the changes in the properties of long-term potentiation in serotonergic and noradrenergic neurons after repeated MDMA exposure [23]. Rat cortical embryonic cortical primary cell cultures were exposed to MDMA and it was found that stem cells and neurons were decreased [24]. Cell viability and cytoskeletal light filament were reduced in rat raphe nuclear cell lines upon treatment with MDMA, but BDNF seems to protect these neurons from the damaging effect [25].

Non-human, Primates, and MDMA Effects

Experiments conducted with MDMA on human primates, *i.e.*, on monkeys for three weeks have reduced the level of presynaptic serotonin markers [26]. Differential electrophysiological firings were noted in brain slices of ventral midbrain dopaminergic neurons exposed to different concentrations of MDMA. At lower concentrations (1 mol/L) MDMA excited the cells, whereas at higher concentrations (10 –30 mol/L) it caused the hyperpolarization of the cell. These higher concentration effects are due to the effects caused by the activation of D2 autoreceptors [27]. The same observation is seen in rats exposed to different concentrations of MDMA. In the hippocampus, there was a significant decrease of neurons in MDMA-exposed rats in comparison to the control and this is due to different dose treatments of MDMA [28]. People may experience trouble concentrating, impaired memory, judgement, difficulty, unable to recognise dangerous situations, and unable to process information in the brain due to the long time effects of heroin. Learning and memory were affected in developing animals which are exposed to MDMA. In mice, MDMA has been shown to cause the loss of dopaminergic cells in the substantia nigra [29].

Mitochondria and MDMA

Mitochondrial trafficking and mitochondrial fragmentation were increased in the hippocampus due to MDMA treatment, indicating mitochondrial involvement [30]. In contrast, the recreational use of MDMA is not doing long-term changes on serotonergic neurons [31]. Compared to control the MDMA-treated group had

CHAPTER 4

LSD (Lysergic Acid Diethylamide)

Abstract: LSD is a potent hallucinogen. It was first synthesised in 1938. It is marketed under numerous names. Ergot, a fungus that develops on rye and grains, is used to make LSD. The effect of LSD is mind-altering, pleasurable, and stimulating. Sometimes, exposure to this drug causes so-called unpleasant experiences, such as “bad trips”. It is classified as a Class 1 drug (highly abused) by the Drug Enforcement Agency. Paranoia or psychosis can occur as a negative sequence of taking LSD. Changes in perception, sense of time and space, and mood are reported due to the use of LSD. This medication can be taken orally or through the tongue using tablets, droplets, or blotter paper. LSD is marketed in the streets as blotter paper, thin squares of gelatin, tablet form, liquid sugar cubes, and pure liquid form. Since this is a mind-altering drug, it causes changes in serotonin levels in the brain. LSD affects one's ability to make rational decisions. Speaking with a healthcare professional, talk therapy, and additional medical therapy are options since there is no medication to treat LSD.

Keywords: Brain , Hallucinogen, LSD, Mind-altering drugs, Paranoia, Psychosis, Serotonin levels .

INTRODUCTION

Swiss chemist Albert Hofmann (1938) synthesized LSD [1] working in the Sandoz laboratories in Basel, Switzerland. LSD, the series' 25th molecule, was discovered to be able to be used as an ergot derivative. Hoffman consumed 250ug and experienced a mixture of dizziness, perceptual distortion, confusion, and a tremendous fear of going insane (Hoffman 2009). LD50 values were calculated for the use of LSD in aminals and they were found to differ from species to species. For example, an LD50 value of 50–60 mg/kg was found in mice, whereas for rabbits, it was found to be 0.3 mg/kg [2]. Cutting-edge neuroimaging studies have revealed the disintegration of cortico-striato-thalamo-cortical (CSTC) pathways to lead to a psychedelic state in LSD users [3].

LSD enhances the effect of MDMA, causing an increase in dehydration and heatstroke. A mixture of LSD with MDMA can cause overdose and death. The effects of LSD start decreasing in 24 hrs and may lead to paranoia, depression,

Jayalakshmi Krishnan

and panic; however, MDMA takes a little more time to demonstrate deteriorating effects. LSD and MDMA, if taken together, can cause various symptoms, such as memory problems, decreased appetite, aggression, irritability, insomnia, and trouble concentrating.

In male mice, the effects of LSD on social behaviour using *in vivo* electrophysiology, optogenetics, behavioral paradigms, and molecular biology, were studied. These studies were carried out to understand glutamatergic neurotransmission in the medial prefrontal cortex (mPFC). LSD promoted social behaviour by activating 5-HT_{2A}/AMPA/mTORC1 in excitatory neurotransmission [4]. Epigenetic changes were observed in the rat prefrontal cortex due to LSD administration [5]. LSD interacts with lysosomal cells in neurons, causing behavioural changes (Hendelman 1972). Upon ingestion, LSD is converted to 2-oxo-3-hydroxy-Lsd by liver enzymes. Serotonin receptors and dopamine receptors are the targets for LSD, in particular, all serotonin receptors and D2 receptors [6]. Serotonin 2B receptor subclass was found to be the receptor for binding of LSD to its diethylamide moiety [7]. Up to 20 micrograms of the drug LSD is enough to exert its effects on humans [8]. 5-HT_{2A} receptor is also known to play an essential role in eliciting the effect of LSD [9].

Neurocognitive Effects

LSD decreases the function of attention and cognition [10], and psychomotor functions are also impaired by LSD [11]. Acute anxiety or depression are the main symptoms after the initial use of LSD [Drug Enforcement Administration (2018); D-Lysergic Acid Diethylamide]. LSD initiates the primary process of thinking *via* activation of 5-HT2A receptors [12]. Memory function is affected by LSD use, which especially leads to the impairment of visual memory [13]. The thinking process and intellectual ability are also compromised by LD intake [14]. The effect of LSD on mood changes has been reported to be concentration-dependent. A low dose of LSD (5 mcg) caused anxiety and confusion at 20 mcg [15]. Risk-based decision-making is not affected by LSD, but it affects working memory, executive functions, and cognitive flexibility [16]. The psychosensory responses of LSD are due to the activation of the 5-HT2A receptors and modulation of 5-HT2C and 5-HT1A receptors [9, 17]. LSD could activate various intracellular singling cascades in the male Sprague-Dawley rats' brains; it has been reported to upregulate genes related to cytoskeletal maintenance, glutamate signaling, and synaptic plasticity [18]. LSD affects the signaling of dopamine neurons through the 5-HT1A, D2, and TAAR1 receptors [19]. Hippocampal place cell firing is reduced greatly under the influence of LSD in rats [20]. Tolerance in rats triggered upon LSD treatment due to the reduced serotonin receptor signals in the rat neocortex [21].

5-HT(2A) receptors in the anterior cingulated cortex and medial prefrontal cortex were activated by LSD, confirming the role of these areas in hallucinations [22]. 5-HT(2A) receptor is also involved in the expression of genes involved in schizophrenic hallucinations caused by LSD [23]. 5-HT(2A) receptor is also involved in activating the MAP kinase pathway by upregulating genes, such as C/EBP-beta, MKP-1, and ILAD-1 in the mammalian prefrontal cortex [17]. Apart from that, LSD is known to activate genes that are involved in synaptic plasticity, cytoskeletal architecture, and glutamatergic signaling [18]. 5-HT2 receptor is involved in the binding of LSD and also other hallucinations, as determined by *in vitro* radiolabeling methods [24]. 5-HT(2A) receptor (2AR) binds with all three hallucinogens, such as mescaline, psilocybin, and LSD, suggesting that in the cortex, these 2AR receptors mediate the behavioural responses [25]. Psychotic actions of LSD are mediated by the binding of LSD to the dopaminergic D2R promoter complex [26]. In interneurons of rat piriform cortex, LSD and phenethylamine were also proven to be potent agonists to the 5-HT(2A) receptor (2AR) [27]. Further studies state that the Ca^{2+}/CaM-KII-dependent signal transduction pathway is involved in mediating the NMDA receptor-mediated hallucinogenic effects by LSD [28]. In the monkey brain, selective binding of LSD was found to be the cause of dopamine-mediated agonistic action in producing hallucinogens [29]. LSD was found to be an agonist for dopamine and serotonin receptors in the central nervous system [30]. Increased activation of serotonin receptors due to LSD is mainly responsible for behavioural syndromes in rats exposed to systemic LSD [31]. Some of the behavioural changes associated with LSD were reported to be due to the influence of both 5-HT2A and 5-HT2C receptors [32].

Organotypic cultures of mouse cerebellum were exposed to LSD and it was found to cause endocytosis and changes in the metabolism of the cells [33]. Brain-derived neurotrophic factors were increased in blood plasma by single low doses of LSD (5, 10, and 20 μg) in healthy volunteers [15]. LSD mediated social behaviour through mTOR pathways, which is the mechanistic target of rapamycin complex 1 in the medial prefrontal cortex, in male mice [4]. LSD (75 μg, intravenously) in healthy volunteers caused psychosis-like symptoms [34]. In male Sprague-Dawley rats treated with LSD, the temporal phase of behavioural changes was mediated by D2 dopamine receptors [35]. Hippocampal-cortical interaction was suppressed by LSD during active behaviour [20]. LSD was found to increase signal entropy by making a gene expression network; this has also been proven by neuroimaging in the human brain [5]. In a D2 dopamine receptor-mediated fashion, LSD modulated the firing activity of reticular thalamus neurons, thereby altering the state of consciousness in humans [36]. However, LSD is known to increase connectivity from the thalamus to the posterior cingulated cortex *via* serotonin 2A receptor activation [3]. LSD-induced visual

CHAPTER 5

Methamphetamine

Abstract: Methamphetamine (METH) is a highly addictive stimulant that affects the central nervous system. It is a widely abused psychostimulant. Monoaminergic neurotransmitter terminals are affected by METH intake. METH structure is very similar to amphetamine, a drug used to treat attention-deficit hyperactivity disorder (ADHD). METH is taken in various modes, such as smoking, swallowing, snorting, injecting powder, *etc*. Dopamine levels, serotonin levels, and norepinephrine levels are increased due to METH uptake, leading to extremely strong euphoric effects. This dopamine surge causes the brain to repeatedly take the drug and is responsible for addiction. As a short-term effect, METH causes increased wakefulness and physical activity, decreased appetite, faster breathing, rapid and/or irregular heartbeat, increased blood pressure, and body temperature. METH overdose causes hyperthermia and convolution, which can lead to death if not treated. METH also causes irreversible brain damage. Amphetamine psychosis, dementia-like symptoms, increased anti-social behaviour, and increased susceptibility to neurodegenerative diseases are the long-term neurological effects of METH use.

Keywords: Amphetamine psychosis, Attention-deficit hyperactivity disorder (ADHD), Dopamine levels, Serotonin levels.

INTRODUCTION

Crystal METH is a more powerful and harmful addictive [1] than amphetamine. Chronic psychosis is the most problematic psychiatric issue during MEH usage [1 - 4]. It has been observed that crystal METH abuse causes disturbances to striatal volume [5]. Diffuse white matter alterations were seen in the temporal, frontal/parietal and occipital lobes in METH users [6]. Dopamine transporter levels were increased **72** hours after withdrawal in rats during methamphetamine self-administration **(2)**. METH stays in the brain for a significantly longer time than cocaine. Due to this reason, the drug has long-lasting behavioural and neurotoxic effects. Moreover, it causes brain damage, heart damage, liver and kidney damage, intense itching, severe tooth decay, and tooth loss. Irritability, anxiety, psychosis, and mood disturbance are the common psychiatric symptoms with METH usage [7]. In Australia, it was found that the prevalence of METH usage is 11 p ercent higher [8]. There is also a dose-related increase in violent

Jayalakshmi Krishnan

behaviour during periods of methamphetamine use [9]. Up to 12 hrs, crystal METH produces euphoria in the brain, causing a high risk of physical and psychological disturbance. Some other drugs are also combined with METH to create a stronger effect. Such drugs are alcohol, morphine, and xanax. Microglia activation is one of the phenomena that lead to METH neurotoxicity [7, 10]. Neurotoxicity of METH causes astrogliosis, tyrosine hydroxylase (TH), metabolite dysregulation and imbalances, *etc* [11 - 13]. In a study, it was found that μ-opioid receptor knockout mice were highly insensitive to METH challenge as they demonstrated a change in dopamine receptor ligand binding activity [14]. Dopamine receptor 3 knockout mice revealed that it sensitises the brain to behavioural changes and gene expression [15]. The key differences between METH and amphetamines are as follows: amphetamines are prescription drugs that are prescribed by doctors. They fall into the category of stimulant drugs and are used in medical science for treating some diseases. However, METH is an illegal stimulant and street drug with no medical use. Both these drugs are classified as Schedule II drugs as they are susceptible to abuse and addiction.

Amphetamines and METH

Amphetamines are used for both therapeutic and recreational purposes, so doctors must educate patients on the potential toxicity of therapeutic and recreational amphetamine use. There are two forms of amphetamines: one is a slow-acting oral form of amphetamine (20–60 minutes), and the other is a fast-acting oral form (seconds to minutes) of amphetamine. Slow-onset form is given for medical purposes, but fast-acting forms are taken under unsupervised medical use [16].

For ADHD children, the typical dose of amphetamine is 20–25 mg. Neurodegeneration and cognitive decline are noted due to the continuous use of METH [17, 18]. It has been observed that methamphetamine users develop Parkinson's disease more frequently than non-users [19]. METH-induced neurotoxicity causes oxidative stress, activation of transcription factors, excitotoxicity, and DNA damage. Not only these, but blood-brain barrier breakdown, microglia activation, and overactivation of various apoptotic pathways are also noted [13, 20]. METH-induced neuroinflammation leads to neuropathology. Catecholamine neurotransmission has been affected due to METH use [21].

Impaired Neurogenesis

It has been observed that dentate gyrus neurogenesis is impaired in METH users, followed by cognitive decline [22]. Moreover, dentate gyrus stem cell renewal is also decreased in METH users. In animal studies, it was found that METH causes neurodegeneration in the dopaminergic nerve terminal, thus reducing the

expression of tyrosine hydroxylase [23, 24]. Furthermore, hippocampal neurogenesis was found to be impaired by METH addiction in mice [25].

Dopamine and METH

It has been observed that dopamine and vesicular monoamine transporters are decreased in the dopamine neuron membrane by methamphetamine [26, 27]. Dopamine and serotonin are the two neurotransmitters that are released by acute METH exposure [28]. METH has various effects on dopamine: 1) competing with dopamine for binding sites, 2) disrupting the storage of dopamine in the vesicles, and 3) triggering dopamine efflux [24, 29, 30]. The specific mechanism of METH dysregulation by dopamine is due to its binding to the SIGMA receptor, which lies in the membrane of the endoplasmic reticulum, which is also a chaperone [31]. METH stays in the brain for a longer time; hence, it exerts its stimulant properties for a long time [32]. METH particularly affects the nigrostriatal pathway, not affecting the mesolimbic pathway [33]. Interestingly, METH is known to activate Toll-like receptor 4, leading to high dopamine levels in the extracellular space, thus paving the way to finding a cure for drug abuse [34].

METH impairs the Ubiquitin Proteasome System (UPS) through dopamine action [35]. Through activating and channelizing intracellular calcium levels, METH causes the release of dopamine [36]. METH users can develop neurotoxic effects, which may be reflected as edema, stroke, haemorrhage, hallucinations, and paranoia. Its withdrawal produces effects associated with anxiety and extreme cravings for the drug. METH users can develop shortness of breath and increased respiration, ultimately leading to heart attack or stroke.

Oxidative stress is induced by METH in the mitochondria of substantia nigra pars compacta dopaminergic neurons [37]. Chronic METH-induced neurodegeneration is due to mitochondrial stress mediated by calcium channels and monoamine oxidase [38]. Chronic METH intake also induces mitochondrial stress in substantia nigra pars compacta (SNc) axons [39]. Tyrosine hydroxylase mRNA levels were altered in rats due to repeated METH administration [40]. METH administration caused long-lasting changes in dopamine neurons of the nigrostriatal pathway [41]. In male mice, METH treatment caused apoptosis in striatal neurons, such as parvalbumin neurons and cholinergic interneurons [42]. Similar observations were made in the striatum that METH intake damaged striatal neurons and dopaminergic terminals [43]. Furthermore, in somatostatin interneurons, METH caused the trafficking of neurokinin 1 receptors, leading to anti-apoptotic activity [44]. Neuronal nitric oxide synthases were induced by METH, as evidenced by 3-nitrotyrosine in the striatum [45].

CHAPTER 6

Morphine

Abstract: Morphine is a Schedule II drug and it is used in pain treatment. Like other opioid drugs, it also has addictive properties. The other street names of Morphine include M, Miss Emma, Monkey, Roxanol, and White Stuff. There are natural alkaloids come from the resin of opium poppy, *Papaver somniferum.* Morphine is attached to the receptors in the brain and spinal cord to block pain signals. Morphine impacts the level of dopamine and serotonin by acting in the brain's reward system. Breathing and heart rate are also modified due to morphine which has both short-term and long-term effects. Morphine can last up to 4 to 6 hours in blood. It also acts on the dendrites and spines in order to change the plasticity of the neurons. Endogenous and exogenous opiates target the same tissues and cells.

Keywords: Alkaloids, Dendrites and spines, Endogenous and exogenous opiates, *Papaver somniferum*.

INTRODUCTION

Opium family of compounds includes morphine and other well-known naturally available or synthesized products such as heroin, codeine, hydrocodone, oxycodone, and oxymorphone. Opioids are used as one of the main drugs used in modern medicine. To alleviate severe pain, opioids are the main drugs used. Synthetic opioids such as Fentanyl, meperidine, methadone, and loperamide are also prescribed for medicinal purposes [1]. In both the adult and developing brain, the use of morphine causes changes in the postsynaptic terminals of the excitatory synapses in the limbic system. In adult zebrafish (*Danio rerio*), morphine exposure leads to increased *oprm1* and *npas4a* mRNA levels in the medial zone of the dorsal telencephalon (Dm), ventral region of the ventral telencephalon (Vv), preoptic area [2].

Moreover, morphine leads to poor thinking ability, changes the activity in the brain stem and spinal cord, alters the brain’s ability to respond to attacks on the microbes, and harms the memory-making process. Both morphine and fentanyl cause increased intracranial pressure and decreased mean arterial pressure and cerebral profusion pressure [3]. Reference memory and working memory were affected in rats exposed to morphine. Emotional reactivity and anxiety were also

Jayalakshmi Krishnan

reduced in the addicted group in comparison with the normal group [4]. Opioid exposure leads to effects on the amygdala, decreased mu-opioid receptor sensitivity, $GABA_A$ receptor modulation, and modifications in glutamate receptor signalling [5, 6].

Prescription of opioids causes structural and functional changes in reward and motivational areas [7]. In addition, cytoskeletal-related proteins are also affected due to morphine exposure in reward-related areas [8]. There was a difference in the brain metabolic state in regions such as cortex, hypothalamus, brainstem, and cerebellum after morphine consumption in Lewis and Fischer 344 rat strains [9]. It was found that the metabolism of Morphine is much higher in the brain areas of reward in the LEW strain than in the F344 strain. Methadone, an opioid affects early mylenation in the developing rat brain [10]. Drugs of abuse can induce C-FOS expression during withdrawal symptoms, and this C-FOS expression can also be correlated with conditioned place aversion, locomotor sensitization, and conditioned place preference (CPP) [11 - 13]. The FOS expression is noted in the central and basolateral amygdala (CeA and BLA), cingulate cortex, nucleus accumbens (NAc), and bed nucleus of the stria terminalis (BNST) [14].

Prolonged morphine taking caused an upregulation of Bax protein and proapoptotic caspase-3 in rats followed by a reduction in antiapoptotic Bcl-2 protein in rats [15] μ-opioid tolerance has been established by the development of opioid tolerance *via* NMDA receptors [16 - 19]. Synaptic balance is disrupted due to morphine use in the hippocampus [20]. Neural pathways of learning and memory are interconnected with addiction pathways. In patients with cancer and healthy individuals, morphine use interferes with learning and memory [21, 22]. Morphine treatment in chronic conditions caused a reduction (25%) in the perimeter of the ventral tegmental area dopamine neurons [23] (D1-receptor (D1R) expressing and dopamine D2-receptor (D2R) neurons in the nucleus accumbans firing ability was altered due to morphine use [24] In animal models, the injection of morphine at sites, medulla, substantia nigra, nucleus accumbens, and periaqueductal gray (PAG) has caused a reduction in pain behaviour [25].

Under medical supervision, injectable morphine is released into the skin, muscles, and veins. However, some users may misuse morphine as like other opioids without proper medical supervision. It's unavoidable for them as they take this morphine regularly even if it is interfering with their personal and professional work. There can be severe withdrawal symptoms if morphine intake is suddenly stopped. Morphine impacts the brain in various ways such as diminished reflexes, reduced neuroplasticity, impairment in psychomotor function, problems in the amygdala, and disrupted brain synapses causing impaired memory. White matter and cerebellar injury were seen in preterm infants in infants with a birth weight

of < 1500 g [26]. In addition, alteration in plasticity was noted in the developing and adult brains in the limbic areas [27].

For opioid disorder methadone (Dolophine) and buprenorphine are the treatment options. Naltrexone (Revia) is another option as it prevents the binding of opioids and blocks their actions. Medication-assisted treatment options can improve survival and reduce opiate misuse. Behavioural therapy includes developing healthy life skills, continuing medications, and changing the attitude of drug misuse. In a model of homocysteine-induced oxidative stress in rat brains, it was shown that morphine increases apoptosis in the hippocampus [28]. Nerve repair and nerve damage in rat models of acute morphine exposure have shown that endoplasmic reticulum stress in the involved [29].

In rat hippocampus and neuroblastoma SH-SY5Y cells, and showed that beclin 1 level are responsible for autophagy [30]. In Morphine tolerance dysfunction of mitophagy is seen and it is due to PINK1/PARKin mediated pathways [31]. Cerebellar brain slices from rats exposed to morphine protected these neurons from ischemia-reperfusion conditions [32]. Microglial activity and neurotoxicity were inhibited by morphine indicating morphine's anti-inflammatory and neuroprotective effects [33]. Morphine tolerance is established by NLTP3 inflammasomes and toll-like receptor 4 [34]. Morphine treatments to microglial cells and neurons have shown that caspase 3 is involved in morphine-induced apoptosis [35]. Another study states that by upregulating microRNA-181-5p morphine induces apoptosis in hippocampal neurons [36]. During pain signalling in lower afferent nociception pathways, it is shown that synapses become sensitive to morphine [37]. In human brain endothelial cells, morphine exposure causes dysregulation of NRF2 pathways and mitochondria dysfunctions [38].

CONCLUSION

Opium family of compounds includes morphine and other well-known naturally available or synthesized products such as heroin, codeine, hydrocodone, oxycodone, and oxymorphone. Opioids are used as one of the main drugs used in modern medicine. To alleviate severe pain, opioids are the main drugs used. Synthetic opioids such as Fentanyl, meperidine, methadone, and loperamide are also prescribed for medicinal purposes [1]. In both the adult and developing brain, the use of morphine causes changes in the postsynaptic terminals of the excitatory synapses in the limbic system. In adult zebrafish (Danio rerio), morphine exposure leads to increased oprm1 and npas4a mRNA levels in the medial zone of the dorsal telencephalon (Dm), ventral region of the ventral telencephalon (Vv), preoptic area. For opioid disorder methadone (Dolophine) and buprenorphine are the treatment options. Naltrexone (Revia) is another option as it prevents the

CHAPTER 7

Ketamine

Abstract: Ketamine is a dissociative anaesthetic drug that functions as a blocker of NMDA receptors. Moreover, it causes a neurostimulatory effect and is also used as a sedative. Ketamine has many names, such as Special K, Green K, Super K, Super Acid, Jet, and Cat Valium. Ketamine is used as a recreational drug in clubs, also known as a "club drug". As a recreational drug, it causes the patient to experience delirium and an altered state of consciousness. Patients with cardiovascular disabilities can also be given ketamine as a sedative. Ketamine can be taken in various methods, such as orally, rectally, intranasally, IV, IM, or intrathecally. Ketamine abuse can lead to secondary renal damage and upper gastrointestinal symptoms.

Keywords: Anaesthetic drugs, Blockers of NMDA receptors, Sedative recreational drugs.

INTRODUCTION

Ketamine is used with other medications or alone as a general anaesthetic agent. It is a cyclohexane derivative and dissociative drug. It binds to NMDA receptors as a non-competitive antagonist. It can also bind to other receptors that are producing anaesthetic effects, ex.opioid, adrenergic, cholinergic, and monoamine receptors [1]. Ketamine is safely used as an anaesthetic agent worldwide in operation theaters for children and adults [2]. In chronic pain management, ketamine is used [3]. In the liver, ketamine is metabolised by N-demethylation and ring hydroxylation pathways [4]. At Parke Davis Laboratories, in 1963, ketamine was developed as a replacement for phencycline as its chemical nature and mechanism are similar to ketamine. Ketamine does not interact with GABA receptors. Norketamine is the major metabolite of ketamine for metabolism in the liver. The half-life of ketamine is 186 min. Ketamine is used in many forms, such as smoking, mixed in drinks, injection, or liquids that can be mixed in liquids. The side effects of ketamine are depression, flashbacks, hallucinations, agitation, and unconsciousness. Tolerance to ketamine can be established by regular usage. Overdose can cause coma and death. Ketamine bladder syndrome can be established in long-term users along with headaches and stomach pain. Regular using of this drug can lead to problems with memory and concentration. Cardiac arrhythmias can happen in people who overdose on ketamine with alcohol or

Jayalakshmi Krishnan

heroin or with other opioids. Memory loss is reported to be the long-term effect of taking ketamine. In the primary somatosensory cortex, ketamine has inhibited the excitatory synaptic transmission of neurons [5]. (HCN1 pacemaker channels were found to be the substrate for the anesthetic effect of ketamine [6]). In another study, it was found that excitability was impaired by ketamine by blocking sodium and voltage-gated potassium currents in superficial dorsal horn neurons [7].

Ketamine as Antidepressant

Ketamine is a N-methyl-D-aspartate receptor (NMDAR) antagonist, and its effect as an antidepressant has been shown in various research articles. On the other hand, by activating the adult-borne immature granule neurons, ketamine alleviated the depression-like symptoms in mice [8]. Yet in another study, it was interesting to note that ketamine at sub-anaesthetic doses has been shown to treat depression in the clinical trials conducted [9]. Oral rapamycin treatment in patients with depression along with ketamine treatment has raised the level of antidepressant-like activity of ketamine. It means rapamycin has been shown to extend the benefits of ketamine [10]. Eukaryotic elongation factor 2 (eEF2) kinase has been deactivated by ketamine resulting in reduced EF2 phosphorylation causing the antidepressant-like property of ketamine [11]. In human patients, treatment with a single ketamine dose has created a rapid and robust antidepressant response [12].

Ketamine as an Anti-inflammatory Compound

The effect of ketamine on neuroinflammatory changes is because of the given dose. Spatial memory recognition was disturbed by ketamine at a dose of 60mg/kg also in mice, it was shown to reduce anxiety-like behaviour [13]. Single administration and long-term administration of ketamine had tremendous effects on the levels of inflammatory markers such as TNFa in mice. A single dose has induced TNFa levels high, but repeated dose has not increased its levels [13]. Locomotor activity was compared between male and female rats. It was found that 10 mg/kg ketamine has been shown to reduce spontaneous locomotor activity in male rats, whereas 40 mg/kg induced locomotor activity in female rats [14]. Ketamine (20 mg/kg) single dose has not prevented neuro inflammation in rats [15]. Treatment-resistant depression (TRD) is a challenge to the medical world. Ketamine has evidently shown to induce anti-inflammatory actions by causing antidepressant activity [16]. After repeated ketamine exposure, TNFa levels were downregulated in patients [5]. LPS-induced delirium neuro inflammation was attenuated by ketamine. Interestingly, in 2019, Esketamine, a nasal spray was approved by the Federal Drug Administration (FDA) to treat depression [17]. There are studies that found that in comparison with other anti-depressants,

ketamine plays a major role in treating depression [18]. Transient receptor potential vanilloid 4 (TRPV4) is known to be involved in various neurodegenerative diseases. C57BL/6 mice were injected with ketamine and proved that ketamine has improved cognitive dysfunction in Perioperative Neurocognitive Disorder (PND) [19]. Ketamine also reduced inflammation in the primary glial cells upon infection with LPS [20]. In rats, it was found that ketamin's effects were seen in reducing depression and this was mediated by the downregulation of proinflammatory cytokines in the rat hippocampus following microglia deactivation [6]

Ketamine Induces Apoptosis in Neuronal Cells

In the rhesus monkey, ketamine has induced cell death *via* the necrotic and apoptotic processes as analysed by electron microscopy. Nuclear condensation and fragmentation were observed in neuronal cells in the rhesus monkey brain [21]. Ketamine at a dose of 1, 10, and 20 μM treatment in hippocampal neurons has shown downregulation of multiple cellular markers [22]. The research also says that an imbalance in calcium signalling pathways in neuronal cells is the main reason for ketamine-induced abnormalities [23]. Moreover, *in vitro* studies have shown that ketamine at a dose of 0, 20, 100, or 500 μM treated for 6 and 24 h in human iPSC-derived dopaminergic neurons disrupted the mitochondrial electron transport system causing autophagy and mitochondrial dysfunction [24] immature γ-aminobutyric acidergic (GABAergic) interneurons were cultured and treated with 5 μg/ml ketamine for 4 hrs. This resulted in alterations in the dendritic growth and the dendritic arbour was impaired. When neural stem cells were treated with ketamine, it caused a significant decrease in viability and reduced proliferation with an increase in apoptosis [25]. Surprisingly, some studies on hippocampal cell lines upon treatment with ketamine have shown an increase in cellular proliferation [26]. On thalamocortical slices, ketamine, it was shown by the patch clamp technique that ketamine suppressed the activity of voltage-gated sodium channels [27].

Adult-born immature granule neurons (ABINs) from the mouse hippocampus when treated with ketamine have shown full activation thus alleviating the depressive behaviour [8]. There are studies that point out that although ketamine causes neural stem cell proliferation, at the same time, it can induce neuronal apoptosis *via* a mechanism involving mitochondrial reactive oxygen species production [28]. In the mouse cerebral cortex, also an apoptosis mechanism was observed after ketamine treatment [29]. In the developing brain in the neural progenitor cells, ketamine alters the neurogenesis process, this finding can be used to educate pregnant women who misuse this drug [30]. Ketamine was found to induce apoptosis in human lymphocytes and neuronal cells at millimolar

CHAPTER 8

Fentanyl

Abstract: Fentanyl is an opioid usually used in general anaesthesia, due to which it is also called an analgesic drug. These drugs can relieve the pain within the body by blocking the neurotransmitters or chemicals that cause pain in the body. Opioids can work in both the ascending pathways of the brain as well as the descending pathways of the brain for pain modulation. Fentanyl is more potent than morphine and herion. Fentanyl is also given as transdermal patches or lozenges in the treatment of pain management. Fentanyl is also sold illegally and can cause of death too when abused. Because of its strong property to be addicted, fentanyl also is mixed with the heroine. Moreover, fentanyl has its own effects during withdrawal, which causes behaviour changes. Fentanyl can bind to μ-opioid receptors (MORs) to exert its effects. In addition, fentanyl abuse is becoming more common globally. Fentanyl causes the brain to suffocate by decreasing the oxygen supply, causing hypoxia and hyperglycemia as well. Fentanyl abuse can cause serious cognitive issues, leading to severe structural damage manifested as hormonal and neuronal disturbances. By suppressing the two brainstem areas, opioids cause disturbances to breathing.

Keywords: Addiction, Decreasing oxygen supply, Hyperglycemia, Opioid, μ-opioid receptors (MORs).

INTRODUCTION

Long-Evans rats, when exposed to fentanyl, showed decreased oxygen supply in the basolateral amygdale as revealed by electrochemical detection [1]. At 3–7 μg/kg dose range, fentanyl causes significant hypoxic effects in human patients [2]. In the dorsolateral pons, due to fentanyl, the respiratory neurons can be affected so breathing is stopped [3]. Fentanyl also causes muscular rigidity by acting on neurons in the area known as locus ceruleus. This area of the brain is responsible for regulating adrenaline levels in the brain. Brain malondialdehyde levels were enhanced by fentanyl treatment [4]. In preterm infants, fentanyl administration protects the developing brain by relieving pain [5].

Fentanyl in the powdered form looks quite similar to other drugs. Fentanyl can be mixed with cocaine, heroin, and methamphetamines. Fentanyl is always mixed with heroin, cocaine, and methamphetamine and sold as pills to look very similar

Jayalakshmi Krishnan

to other prescription opioids. Lacing fentanyl with other drugs is often lethal but the users are unaware of this.

Hippocampus and Fentanyl

In the Schaffer-collateral CA1 pathway in the hippocampus, fentanyl treatment disturbs long-term potentiation and enhances long-term depression [6]. Apart from this, fentanyl at lower concentrations, such as 0.01 and 0.1 μM, can decrease AMPA receptors and cause the destruction of dendritic spines in cultured hippocampal neurons. As the hippocampus plays an essential role in memory, this effect can cause problems in memory storage [7]. Not only that opioids when administered chronically caused the impairment of cognitive function [8], but cortical neurons, and glial cells, were co-cultured and treated with low (0.01 μM) and high (10 μM) doses of fentanyl caused gene expression changes in the synaptic plasticity property [9]. Moreover, this kind of exposure to fentanyl also damages somatosensory circuit behaviour and functions [10]. During early development periods, in the 2nd and 3rd layer of somatosensory neurons, male and female C57BL/6J mice, when given environmental enrichment, have shown changes in function [11].

Neurotoxic Effect of Fentanyl

Some studies point out that not only the adrenaline level but also the glutamate neuronal network is involved in the muscular rigidity caused by fentanyl [12]. By using extracellular recordings, the rat brain slice preparation has been used to understand the effect of serotonin and noradrenaline (NA), on nociception during fentanyl and morphine treatment. The firing activities of these opioids are inhibited by fentanyl and morphine treatment as well [13]. Fentanyl was found to be neurotoxic to spinal cord neurons [14]. Fentanyl also acts on the GABAergic neurons in the vagus nerve to increase parasympathetic neurotransmission by decreasing GABAergic transmission [15]. This kind of inhibition was seen in both the pre- and postsynaptic neurons.

Noradrenaline and Fentanyl Receptors

In two types of cells, such as human neuroblastoma SHSY5Y and rat phaeochromocytoma PC12, exposure to fentanyl caused a decrease in noradrenaline uptake [16]. There are studies that fentanyl not only acts as amu–opioid receptor but it also acts as an agonist on the 5-HT1A receptor. Fentanyl overdose can also be due to this effect of binding to both receptors [17]. There are a number of evidence that opioids cause disturbances to adult neurogenesis in the dentate gyrus region of the hippocampus, leading to the cessation of differentiation and maturation process in the hippocampus [18].

Mitochondria Damage and Fentanyl

Neuroblastoma/glioma hybrid cell line was investigated for the effect of fentanyl, methadone, and morphine if they cause changes in mitochondrial function. The mitochondrial network was decreased by fentanyl and methadone treatment but not by morphine [19]. In glioma cells, there are reverse findings that morphine causes changes in the mitochondrial membrane potential but not methadone and fentanyl [20]. In the nucleus accumbens (NAc) there are changes in the mitochondrial copy number that are reflected in blood leukocytes as well [21]. In the human neuroblastoma cell line SH-SY5Y, it was demonstrated that fentanyl causes cell death by both necrosis and apoptosis mechanisms [22]. When human hepatoma HepG2 cells were exposed to fentanyl, it was found that mitochondria were greatly affected, which means the respiration rate of mitochondria was affected [23].

Fentanyl and Pain-related and Responsive Areas –PET Studies

Positron emission tomography (PET) studies have shown that fentanyl in human subjects has reduced the blood supply to the thalamus and posterior cingulate cortex [24]. Fentanyl significantly and selectively affects the cerebral brain areas that are associated with pain-related and responsive areas [25]. Mid-anterior cingulate cortex area is activated during fentanyl administration as revealed by PET imaging in human subjects. So this part of the brain may be involved in the fentanyl-mediated analgesic effects [26]. Pain-related areas and pathways in the cingulate cortex and orbitofrontal cortex have shown an increase in the regional blood supply during fentanyl administration in human subjects. These areas are responsible for addiction, nociception, and reward behaviours. Some of the studies point out that Fentanyl administration increased cerebral blood perfusion (CBP) in brain areas where mu-opioid receptors are present [27]. This study is further supported by another study that remifentanil administration has increased the blood supply to areas where mu-opioid receptors are present. In contrast, the primary somatosensory cortex has shown less activation as it contains lower mu-opioid receptors [28]. Fentanyl withdrawal is dangerous as it increases anxiety-like behaviour [29]. Male rats prefer fentanyl than food choice, indicating even in humans, men are more addictive to fentanyl than women [30]. Fentanyl causes respiratory depression, in turn leading to hypoxia and hyperglycemia leading to changes in brain metabolism and temperature in rats [1]. In rats exposed to fentanyl, electroencephalogram, and auditory evoked potentials were changed during fentanyl treatment [31]. There are studies that prove that heroin contaminated with fentanyl causes brain hypothermia and brain hypoxia. Fentanyl-induced seizures cause changes in the brain and cerebral blood flow in rat brains. Nucleus accumbent mediates the behavioural changes associated with

CHAPTER 9

Alcohol

Abstract: Alcohol affects brain activity in various ways. It has both short-term and long-term effects. It causes slurred speech, short-term memory dysfunctions hallucinations, *etc.* by timing the activity of neuronal cells. Moreover, it causes teratogenic effects in the fetus ifthe mother is consuming alcohol during pregnancy. Alcohol can damage the brain cells, cause a lowering of serotonin levels, and higher GABA levels, cease new brain cells to be formed, and cause damage to the blood vessels and nerve cells in the brain. In addition, alcohol abuse causes Wernicke-Korsakoff's syndrome, which is due to the lack of vitamin B1 in drinkers. Also, alcohol abuse causes Wernicke's encephalopathy which is characterised by muscle problems, being confused, *etc*. Memory loss and less coordination are the long-term effects of alcohol abuse. All regions of the brain, such as the cerebellum, limbic system, and cerebral cortex, can be affected by alcohol abuse. The cerebellum is responsible for the movement of the body, and alcohol disrupts this balance causing emotional and memory issues. Alcohol consumption on a regular basis leads to reduced brain size or a rapid aging process. Alcohol disorder is listed as one of the most prevalent mental health problems in the world.

Keywords: Alcohol disorder, Memory loss and less coordination, Serotonin levels, Teratogenic effects in the fetus.

INTRODUCTION

A study conducted in Russia states that vodka use is the major risk factor for death for various reasons in young adults [1]. Mental disorders, cognitive dysfunctions, dementia, and learning and memory defects are common in alcohol users. Alcohol is a depressant; it should be withheld from children and people under the age of 18. Alcohol is very harmful to the developing brain. It can cause the developing brain to be affected in such a way that problem-solving skills will be affected. Seizures, stroke, and dementia are common problems due to alcohol usage. Alcohol also causes damage to the dendrites, which are branch-like structures arising from brain cells. The brain scans of alcohol abusers have shown a high reduction of grey matter volume. Excessive alcohol consumption also causes neurodegeneration. Alcohol use disorder (AUD) is a disorder caused by excessive alcohol abuse causing emotional disturbances. AUD has vast effects on

Jayalakshmi Krishnan

neuronal cells in terms of disturbed synaptic contact, blood-brain barrier dysfunction, demyelination, dementia, *etc.* [2]. Dementia is characterised by psychological changes caused by chronic alcohol use [3]. Acetaldehyde is a metabolite of alcohol, and when the brain cells are exposed to this metabolite, a decrease in growth factors is observed that are leading to neuronal death or degeneration [4]. Alcohol suppresses the communication between nerve cells. Alcohol increases chloride ion conductance inside the cells, making it more negative. Because it binds with the GABA receptor, it opens the chloride ion channels to allow more negative charge inside the cell which the cell becomes a hyperpolarised state. An individual who depends on alcohol can also develop a tolerance to alcohol as it causes intoxication. Alcohol abuse also causes a person to lose social life, loss of jobs, loss of interpersonal skills, liver failure, neurotoxicity, *etc.* [5]. By AUD, 3.3 million annual deaths have been reported by WHO due to alcohol neurotoxicity. In human postmortem brain samples, at the dentate gyrus and subgranular zone, it was shown that persons who died from going alcohol abuse have reduced the number of neurogenic pools *i.e.*, stem cell pools [6]. Abstinence from alcohol causes the brain to revert to its neurogenesis process. Prolonged alcohol intake disrupts the excitatory neurotransmitter pathways [7]. Cytokines and proinflammatory mediators are released in response to binge ethanol treatment under TLR4 activation in adolescent mice.

Role of Toll-like Receptors in Ethanol-induced Changes

There are studies in which alcohol is known to activate microglia and astrocytes through toll-like receptors leading to neuroinflammation [8]. The behavioural and cognitive dysfunction associated with alcohol is due to the epigenetic changes caused by TLR4 activation [9]. There are evidences that scute exposure to ethanol in TLR4++ mice causes microgial cell activation in the brain in comparison with TLR4(-/-) mice. Ethanol induces the expression of TLR4 and TLR2 in microglial cells causing inflammation [10]. Another mechanism by which ethanol activates the TLR is due to TLR4/IL-1RI responses leading to inflammation [11]. Mice defect in TLR4 is protected from various kinds of molecular and behavioural changes, thus further confirming that TLR plays a role in inflammation [12]. In line with the same observations, it was found that TLR 4 knockout mice were prevented from autophagy during ethanol treatment [13]. Ethanol-induced brain damage is due to the recruitment of TLR4/IL-1RI to membrane lipid rafts, causing inflammatory activation [14]. Signaling of these receptors is known to cause cell death in astrocytes treated with ethanol [15]. These receptors are endocytosed in lipid rafts in astroglial cells [16]. Clathrin-dependent pathways or lipid raft caveolae are involved in this type of endocytosis mechanism [9]. When adolescent rats are exposed to high doses of ethanol neuroimmune changes and myelin changes do happen [17]. In the rat hippocampus, SUMO-specific protease

6 (SENP6) and TLR4 are involved in ethanol-induced neuroinflammation [18]. TLR4 activation causes impairment of ubiquitin pathways in mice treated with ethanol in the cerebral cortex [19]. Astrocytes-derived extracellular vesicles are involved in TLR4-mediated neuroinflammation in cortical neurons and astrocyte cultures [20]. In alcohol-fed WT and TLR4(-/-) mice, It was demonstrated that Blood Brain barrier was damaged due to the infiltration of leukocytes [21]. This is mediated by TLR/NLRP3 neuroinflammatory responses.

Ethanol and Animal Studies

In order to under the effect of ethanol on adolescent brains, male rats were treated with different doses of ethanol such as 1.0, 2.5, or 5.0 g/kg, i.g. The brains of these rats have shown in the dentate gyrus there was a reduced neurogenesis [22]. Sprague-Dawley rats (8-12 g/kg/d) were exposed to ethanol for 4 days. The perfused brain samples revealed impaired neurogenesis and brain damage in the cortico-limbic region [23]. In developing rat brains, it was found (GD 17.5) that ethanol causes apoptotic neurodegeneration in hippocampal and primary cortical neurons [24]. Cytotoxic edema was also found to be associated with chronic ethanol exposure in rat brains [25]. Alcohol introduction after abstinence in rat models causes oxidative stress and it induces neuroinflammation [26]. Tyrosine hydroxylase is an enzyme responsible for dopamine synthesis. The levels of this enzyme were higher in the ventral tegmental area of Sprague-Dawley rats. This finding can be useful to understand the rewarding properties of ethanol in the rat brain [27]. Adolescent male Wistar rats exposed to ethanol have shown motor impairments in the open field, behavioural tasks, and cerebral cortex damage [28]. Neurodegeneration and cognitive defects were noted in preclinical rat experiments [22]. Neuronal loss is also noted in the prefrontal cortex of the brain due to alcohol exposure. The evidence suggest that α-Synuclein is involved in the structural changes associated with alcohol exposure in the human brain [29]. Brain atrophy is also another effect of alcohol relapse in patients, especially in areas with behavioural control [30]. There are studies that found that neurotransmitter diffusion is also hampered in the brain due to chronic alcohol consumption [31]. Ethanol causes physical dependence in rats after abstinence for days [32]. This is due to the effect of ethanol on brain ribosomes causing altered protein synthesis [33]. Further studies state that mRNA binding sites in ribosomes are affected due to ethanol intake which leads to tolerance [34]. Mice developing tolerance to ethanol, effects were seen in the orbitofrontal cortex (OFC) of the neurons [35]. Altered long-term potentiation in the medial prefrontal cortex of mice exposed to ethanol was also noted [36]. Toll-like receptor-mediated neuroinflammation is also involved in brain injury following ethanol exposure [21]. In the anterior lobe of the cerebellum, there was a reduction in Purkinje cells in rats when exposed to ethanol [37]. Gliosis induced by ethanol in the rat brain

CHAPTER 10

Nicotine

Abstract: Nicotine is present in the tobacco products. Once smoked, nicotine immediately reaches the brain and binds with nicotinic receptors causing damage to the brain cells. The adolescent brain is especially very sensitive to products such as e-cigarettes, nicotine, and tobacco. Chronic nicotine exposure causes permanent brain damage and cognitive decline. Interestingly there are reports on the use of nicotine and its effects on the epigenetic changes in the brain. These kinds of changes may prepare the brain for further abuse of various illegal drugs. As a result of chronic nicotine exposure brain infarcts, white matter hyperintensities, brain atrophy, and dementia are also known to occur. Neurodevelopment in children is potentially harmed due to exposure to nicotine and nicotinic products. This is due to the inflammation, atherosclerosis, and oxidative stress to the neuronal cells. Pregnant mothers and people who are at risk of developing neurodegenerative disease need to be forbidden from using nicotine. Nicotine can be dangerous when taken with alcohol as it can lead to depression and neurocognitive decline. This chapter addresses the effects of nicotine on the adolescent and adult brain.

Keywords: Brain atrophy, Cognitive decline, Depression, Neurodevelopment, Oxidative stress.

INTRODUCTION

Nicotine is a product from tobacco that is consumed as different products such as E-cigarettes and smoking. Nicotine is a plant-based alkaloid that binds with the acetylcholine receptors in the brain and mimics the effects of acetylcholine. Not only CNS disorders, smoking tobacco by various methods causes various diseases such as cancer, cardiovascular diseases, and respiratory diseases. Nicotine not only influences the acetylcholine receptors in the brain but also has an impact on dopamine, serotonin, and norepinephrine. When these neurotransmitters are affected it leads to cognitive, motor, learning, and memory dysfunctions, especially the executive functions. The reinforcement of smoking initially is due to the enhancement of cognitive enhancement especially attention and memory, however, at later stages, it leads to cognitive impairment and cognitive decline [1].

Jayalakshmi Krishnan

Nicotine in the Ageing Brain

Brain ageing is a very complicated process. The ageing brain displays various changes in its morphology, biochemistry, and physiology. Brain ageing due to reductions in acetylcholinergic pathways (degradation of neurons in the nucleus of myenert) may lead to the development of oxidative stress, beta-amyloid toxicity, calcium-related singlaing dysfunctions, reduced neurotrophic factors, neuroinflammation, and apoptosis. In this condition, smoking by old age persons will lead to the destruction of molecular pathways and dysregulation of nicotinic Acetylcholinergic pathways [2]. However, some studies on animals suggest that nicotine can be neuroprotective instead of neuro-damaging. Activation of nicotinic acetylcholine receptors can improve memory and learning [3]. Controversially, some studies have shown that smoking helps a little delay in developing neurodegeneration.

Nicotine and Fetal Brain Development

Smoking during pregnancy can lead to devastating effects on the developing fetus. Some fetal neurodevelopmental disorders are due to the nicotine smoking by pregnant mothers. The US Food and Drug Administration agency has classified nicotine as a class drug during pregnancy. Pregnancy-related morbidity and mortality is most of the time due to smoking cigarettes or tobacco products. Nicotine leads to reduced blood flow to the placenta leading to cardiovascular dysfunctions, which has been proved by animal studies. Smoking replacement therapy (NRT) during pregnancy has not been well studied [4].

Nicotine and Adolescent Brain

Inhalation of tobacco products can cause other comorbid situations such as anxiety disorders, mood disorders, and Schizophrenia. People with these disorders when consuming tobacco lead to various modulations in the brain circuits. Nicotine influences various neurotransmitters such as GABA, Glutamate, and Dopamine all these neurotransmitters are implicated in various neurodegenerative disorders. Largely, it has been observed that many neurological disorders such as neuropsychiatric disorders are developed either during the developmental period or during the adolescent time of development [5]. The mesocortical limbic system is influenced by mood and anxiety-related symptoms due to exposure to nicotine during adolescence time. The studies performed in rats during adolescence time confer the long-lasting changes in the mesolimbic system and involve disturbances in PFC DA D1R and downstream extracellular-signal-related kinase 1-2 (ERK 1-2) pathways [6]. The nucleus accumbent shell is important for emotional processing. Any disturbances in this structure will lead to the development of mood and anxiety-related disorders. Using an adolescent rat

model several molecular markers which are related to nicotine exposure were examined. ERK 1-2 and Akt-GSK-3 levels were much higher in the adolescent brain but not in the adult brain [7]. Further studies on rats reconfirm that maternal deprivation stress induced the rats' drug-seeking behaviour affecting the amygdala and ventral tegmental area in the brain [8]. Cognitive and emotional disturbances were noted in rodents exposed to prenatal nicotine exposure thus in turn affecting the glutamate receptor-associated genes in the prefrontal cortex [9]. Nicotine abuse in the brain is attributed to the mesolimbic dopamine system, thus affecting the reward stimuli and sensory systems in the early stages of addiction.

Nicotinic Acetylcholine Receptors (nAChRs) in Addiction to Tobacco Smoking

Nicotine's ability to enhance dopamine firing is due to its binding to various subtypes of nicotinic receptors such as alpha 6 [10]. Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels spanning across the membrane with five subunits. α4 and β2 subunits are considered as the predominant subunits of the nAChRs.Almost all subunits of the nAChRs are involved in addiction due to tobacco smoking. α4β2* nAChRs i the main therapeutic target for the approved drugs against the cessation of smoking [11]. There are twelve α subunits (α2-α10) and three beta subunits (β2-β4) of nAChRs in mammalian brain. The receptors such as α4β2 nAChRs, play a very important role in reinforcing qualities of the nicotine, particularly in the mesoaccumbens dopamine pathway. Cloning studies have revealed the genes located in chromosome 15q25, which encode the α5, α3, and β4 nAChR subunits show a particular pattern of genetic variation.

CONCLUSION

Nicotine is a product from tobacco that is consumed as different products such as E-cigarettes and smoking. Nicotine is a plant-based alkaloid that binds with the acetylcholine receptors in the brain and mimics the effects of acetylcholine. Not only CNS disorders, smoking tobacco by various methods causes various diseases such as cancer, cardiovascular diseases, and respiratory diseases. Nicotine not only influences the acetylcholine receptors in the brain but also has an impact on dopamine, serotonin, and norepinephrine. Brain aging is a very complicated process. The aging brain displays various changes in its morphology, biochemistry, and physiology. Brain ageing due to reductions in acetylcholinergic pathways (degradation of neurons in the nucleus of myenert) may lead to the development of oxidative stress, beta-amyloid toxicity, calcium-related singlaing dysfunctions, reduced neurotrophic factors, neuroinflammation, and apoptosis. In this condition, smoking by old age persons will lead to the destruction of molecular pathways and dysregulation of nicotinic Acetylcholinergic pathways.

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

R

S

T

U

V

W

Jayalakshmi Krishnan

Prof. Jayalakshmi Krishnan completed her postdoc training from the Ajou University in South Korea from 2006 to 2008. She received her Ph.D. degree from the DRDO, Delhi, between 2002 and 2006. She has served as a research assistant professor at the Ajou University, South Korea from 2008 to 2009, and later at the SRM University, Chennai, in 2011. She has worked as an assistant professor in the Department of Life Sciences, Central University of Tamil Nadu, from 2012 to 2022, and thereafter at the Department of Biotechnology, Central University of Tamil Nadu, till date. She has served as the head (in-charge) of the Department of Life Sciences from 2012 to 2016. During her tenure as the coordinator of the Department of Epidemiology and Public Health, she has organized various scientific and outreach programmes on vector control, including the WHO Expert Meeting for Kala-Azar Elimination in 2016. She was the key organizer of the 13th International Conference on Vector Borne Diseases in 2017 that was held in Chennai. She has vast expertise in organizing scientific workshops and various outreach activities at the university. Prof. Krishnan has supervised one Ph.D. in the field of entomological surveillance and insecticide resistance, and supervised 19 master students in the area of medical entomology. She has completed two projects for the ICMR and TIGS on vector surveillance at the Lakshadweep islands. Her teaching area includes neurobiology, vector biology, and vector control and management.