Review on major bio chemicals and pathways involved in addiction

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Abstract

Drug addiction is a chronic disease defined by a complex set of characteristics, including loss of control over drug intake and persistent drug craving, which primarily affects a small percentage of people who try drugs. Corticotropine releasing factor CRF plays an important role in the hormonal, autonomic, and behavioral responses to stressors. These psychostimulant drugs interact with monoamine transporters, increasing extracellular 5-HT, dopamine, and noradrenalin activity in the brain. Gamma aminobutyric acid (GABA) is a central nervous system inhibitory neurotransmitter. Changes in the GABA system can affect the functions of reward-related dopamine pathways as well as drug addiction. Dopamine and norepinephrine, which are known to be involved in drug addiction, innervate BNST. Upregulation of kappa-opioid receptors (KOPr; encoded by OPRK1) and their endogenous agonists, dynorphin peptides (encoded by PDYN), plays different roles depending on the stage of an addiction cycle (initiation, withdrawal, or relapse). Single-nucleotide polymorphisms (SNPs) in OPRK1 and PDYN are obvious candidates for involvement in drug addiction susceptibility. Rodents with chronic cocaine administration have lower levels of accumbal glutamate, whereas drug-seeking reinstatement is associated with increased glutamatergic transmission. There are three pathways: 1) the dopamine-related reward system, 2) the oxytocin-related affiliation system, and 3) the glucocorticoid-related stress response system.

Keywords: Addiction, CRF, 5-HT, Dopamine, Noradrenalin, GABA, BNST, Dynorphin, Oxytocin, Glucocorticoid

Introduction

Opioids, such as heroin, morphine, and pethidine (meperidine), are narcotic substances that have inhibitory effects on the CNS, particularly the sensory cortex, resulting in pain relief [1] as a result of actions at the ascending and descending pain pathways. Opioid addiction is regarded as one of the most severe, prevalent, and difficult to treat. This is due to morphine's indirect effect on dopamine receptors, in which the activation of opioid receptors reduces the activity of GABAergic receptors, which

gives inhibitory effect on dopaminergic neurons. This results in an uncontrollable release of dopamine as well as the manifestation of euphoria.[1] Addiction is a complex phenomenon with serious social, economic, and health implications. Opioid addiction has been shown to cause mood disturbances as well as anxiety, depression, and cognitive impairments. Opioid abuse leads to deficits in learning, memory, attention, reasoning, and impulse control.[2] Opioid ligands' physiological and pharmacological effects are primarily mediated by -opioid receptor activities in the brain's mesocorticolimbic pathway. The - receptor contributes to the hedonic properties of opioid agonists, natural rewards, behavioural motivation, and emotion regulation. The ventral tegmental area (VTA), which is located in the midbrain, is the primary site of action for opioid.[3]

Epidemiology

In recent years, the misuse of prescription opioids in the United States has resulted in what is now known as the "opioid epidemic," a public health crisis costing the US healthcare system $26 billion and resulting in 16,000 deaths in 2013. (Florence et al., 2016). Identifying addiction markers can help identify those at risk and reduce fatalities. With a relapse rate of 40–60% (National Institute on Drug Abuse [NIDA], 2020), achieving personalised and effective treatment options is a pressing issue.[4] According the National Survey of Drug Use and Health, in 2019, 57.2 million people aged ≥12 used illicit drugs in the past year. This represents an increase in percentage of people using illicit drugs, increasing from 17.8% in 2015 to 20.8% in 2019. The most commonly used illicit drug in the past year was marijuana, which was used by 48.2 million people, and increasing rates of cannabis use in adults aged ≥26 appears to be a driver for the noted trend of overall increase in illicit drug use. Adolescents aged 12 to 17 had similar estimates of illicit substance use in 2019 compared to 2015 and 2018, with 17.2% of this age demographic using illicit drugs in the past year.[5]

Major bio chemicals involved in addiction

1.CRF

CRF plays an important role in the hormonal, autonomic, and behavioural responses to stressors. In the dark side of addiction, emphasis is placed on the role of CRF in extrahypothalamic systems in the extended amygdala, including the central nucleus of the amygdala, bed nucleus of the striaterminalis, and a transition area in the shell of the nucleus accumbens. The urocortin/CRF(2) systems have received less attention, but findings suggest that they play a role in the neuroadaptation associated with chronic drug use, sometimes in opposition to the effects of the CRF(1) receptor. According to compelling evidence, the

CRF stress system, including its activation of the hypothalamic-pituitary-adrenal axis, plays a critical role in initiating and maintaining dependence. Understanding the role of CRF systems in addiction provides not only insight into the neurobiology of the dark side of addiction, but also novel targets for identifying vulnerability to addiction and treating addiction.[6]

2. Dopamine

Dopamine (DA) regulates processes such as reward, motivation, movement, working memory, and cognition (Chinta& Andersen, 2005). The midbrain dopaminergic neurons, which include the substantia nigra (SN) and ventral tegmental area, are the primary source of DA in the brain (VTA). The dopamine transporter (DAT) is a transmembrane protein found on dopaminergic neurons that takes up DA released into the extracellular space. Dopamine (DA) regulates processes such as reward, motivation, movement, working memory, and cognition. Cocaine raises extracellular DA levels by inhibiting DAT and preventing DA reuptake. [7]

3. Serotonin

Serotonin1A-receptors (5-HT1A-Rs) are critical components of the brain's 5-HT system. They control the activity of 5-HT neurons as somatodendritic auto receptors and the activity of terminal areas as postsynaptic receptors. These psychostimulant drugs interact with monoamine transporters in the brain, increasing extracellular 5-HT, dopamine, and noradrenalin activity. The increase in 5-HT, which, along with dopamine, is a key mechanism in drug addiction, hyperactivates 5-HT1A-Rs. The progress made in this field demonstrates that brain 5-HT1A-Rs play a critical role in virtually all behaviours associated with psychostimulant addiction. Importantly, pre- and postsynaptic 5-HT1A-R contributions can be separated and frequently act in opposite directions. 5-HT1A-autoreceptors primarily facilitate psychostimulant-related behaviours by limiting the 5-HT response in terminal areas. Postsynaptic 5-HT1A-Rs, on the other hand, primarily inhibit the expression of various addiction-related behaviours. 5-HT1A-Rs play an important role in controlling brain 5-HT activity and spontaneous behaviour, but they also play a complex role in regulating the psychostimulant-induced 5-HT response and subsequent addiction-related behaviours. [8]Serotonergic psychedelics or classic hallucinogens are described as substances capable of altering thought, perception, and mood, without memory impairment, delirium, or addiction, with activation of the serotonin (5-HT) 2A receptor (5-HT_{2A}R) as a main pharmacological mechanism.[9]

4. GABA

Gamma-aminobutyric acid (GABA) is a central nervous system inhibitory neurotransmitter. Synaptic plasticity, learning, and memory are all controlled by the GABA system. Animal models and clinical studies have provided evidence that the GABA system is involved in drug addiction. Heroin primarily stimulates dopamine release in the ventral tegmental area (VTA) and nucleus accumbens (NAc), which are modulated by the GABA system . Changes in the GABA system have been shown to alter the functions of reward-related dopamine pathways and modulate drug addiction .The GABA system may be an appropriate pharmacotherapeutic target for the treatment of drug addiction, and variants of this system may also influence treatment response. A growingnumber of experiments support the idea that GABA-related compounds may attenuate the acute reinforcing effects of cocaine, heroin, nicotine and alcohol in rats; a small number of clinical reports also point to beneficial effects withcocaine addicts and alcoholics.[10,11]

5. Norepinephrine

Cocaine raises extracellular norepinephrine levels by inhibiting the norepinephrine transporter and increases dopamine levels in dopamine transporter deficient mice , implicating norepinephrine signalling in psychostimulant-mediated modulation of dopamine function. Indeed, conditioned place preference, escalated cocaine intake by self-administration, and reinstatement of cocaine seeking are all dopamine-dependent behaviours elicited by cocaine . Noradrenergic nuclei project to the ventral midbrain and form synaptic connections with dopaminergic neurons . Noradrenergic nuclei lesions reduce dopamine release in projection areas , whereas stimulation of noradrenergic nuclei excites dopaminergic neurons in a way that is inhibited by systemic administration of 1 adrenergic receptor antagonists . However, the site of action and the mechanism by which norepinephrine signalling mediates cocaine effects are unknown. As a result, we investigated the mechanism by which cocaine mediates increased locomotor activity and increased dopaminergic neuron activity via the 1 adrenergic neurotransmitter in the midbrain, neurotransmission occurs.[12]The bed nucleus of striaterminalis (BNST) is a complex limbic area involved in neuroendocrine and behavioural responses, particularly stress response modulation. Dopamine and norepinephrine, which are known to be involved in drug addiction, innervate BNST. Several drugs of abuse are also known to increase dopamine transmission in the BNST, but there has been less research on the effect on norepinephrine transmission. The microdialysis technique was used to investigate the effect of various drugs of abuse on norepinephrine transmission in the BNST of freely moving rats. Nicotine (0.2-0.4 mg/kg), cocaine (2.5-5 mg/kg), amphetamine (0.25-0.5 mg/kg), and

ethanol (0.5-1.0 g/kg) all increased norepinephrine output dose-dependently, while morphine at 3.0 mg/kg had a lower effect than morphine at 1.0 mg/kg. These findings suggest that, despite having different mechanisms of action, many drugs of abuse have the property of increasing norepinephrine transmission in the BNST.[13]

6. Dinorphine

Upregulation of kappa-opioid receptors (KOPr; encoded by OPRK1) and their endogenous agonists, dynorphin peptides (encoded by PDYN), plays different roles depending on the stage of an addiction cycle (initiation, withdrawal, or relapse). The KOPr/DYN system may also contribute to co-morbid anxiety and depression, both of which have the potential to be used in the treatment of specific drug addictions and psychiatric co-morbidity.[14]

7. SNP

Single-nucleotide polymorphisms (SNPs) in OPRK1 and PDYN are obvious candidates for involvement in drug addiction susceptibility. The SNP rs1051660 (36G>T, exon 1) in OPRK1 showed a point-wise significant association with HD. The SNP rs6473797 (intron 2) was found to have a possible link to heroin and alcohol addiction. At -1986 bp upstream of the translation start site, the SNP rs35566036 (promoter region), 830 bp/indel, was discovered. In HepG2 cells, the insertion allele reduced transcription activity. This indel was strongly linked to alcoholism.

PDYN contains 1-5 copies of a 68-bp variable-number tandem repeat (VNTR) that is located -1250 bp from the translation start site and contains a putative activator protein-1 (AP-1) transcription complex binding site. There was a significant association in HD. The SNP rs1997794 (promoter region) regulates PDYN expression and is linked to alcoholism. The SNP rs1022563 (3' flanking region) was linked to opioid addiction in women but not in men.[14]

8. Glutamate

Cocaine addiction is characterised by an overwhelming desire for the substance, which drives its continued use despite negative consequences. Animal models suggest that addiction-like behaviour is caused by a disruption in glutamate homeostasis in the nucleus accumbens. Rodents with chronic cocaine administration have lower levels of accumbal glutamate, whereas drug-seeking reinstatement is associated with increased glutamatergic transmission. They discovered significantly lower basal glutamate concentrations in the nucleus accumbens in cocaine addicts (N = 26) compared to healthy people (N = 30), as well as increased glutamate levels during cue-induced craving in cocaine addicts compared to baseline. A disruption in accumbal glutamate homeostasis is a key neurometabolic feature of cocaine

addiction in humans. As a result, the glutamatergic system is a promising target for the development of novel pharmacotherapies, as well as a potential biomarker for a personalised medicine approach to addiction treatment. [15]

Drug Addiction-Related Pathways

1. The dopamine-related reward system

The hypothalamus produces oxytocin (OT), a neuropeptide that is important in reward, social affiliation and bonding, associative learning, memory, and stress responses. There is now compelling evidence that OT may be a viable treatment option for the maladaptive processes associated with addiction. In marijuana addicts, OT inhibits opioid tolerance, reduces opiates self-administration, and reduces craving and stress response. There is also a negative relationship between plasma OT levels and novelty seeking, as well as increased negative affect and stress in various types of drug abuse. Abstinence from heroin causes a negative affective state characterised by dysphoria, irritability, anxiety, and abnormal stress reactivity, which drives drug seeking behaviours. Dehydroepiandrosteronesulphate (DHEAS) may buffer the effects of cortisol and contribute to resilience and successful stress adaptation. Cortisol and DHEAS, particularly the cortisol/DHEAS ratio, are being studied as neuroadaptive stress hormones to predict health outcomes. Given the well-established link between stress, drug use, and relapse, as well as the known dysregulation of hypothalamic pituitary adrenal (HPA) axis activity in substance-use disorders, the effects of OT on the stress system have gotten a lot of attention. [16]

2. The oxytocin-related affiliation system

Stress may influence mesolimbic neurotransmission, resulting in altered responses to psychoactive substances, increased susceptibility to addiction, and a greater proclivity to develop affective disorders . Endogenous CART (Cocaine- and Amphetamine-Regulated Transcript) peptide is one of the factors involved in the regulation of dopamine signalling and is expressed in many regions of the mesolimbic system (nucleus accumbens, ventral tegmental area, amygdala) and hypothalamus . CART is thought to participate in a variety of central nervous system processes, including stress response, anxiety, depression, reward, and addiction, most likely by inhibiting dopaminergic neurotransmission.

Neuroplastic adaptations within the mesolimbic dopamine system contribute to complex alterations in reward processing during the transition from recreational substance use to addiction . Both increased mesolimbic sensitivity to drug-related reward signals and decreased mesolimbic sensitivity to non-drug related rewards contribute to dysfunctional decision making and the characteristic narrowing of interests . Drug seeking and consumption compulsively dominate behaviour at the expense of previously rewarding

ones such as social activities or hobbies. This maladaptation manifests itself at the neural level as increased activity in reward regions such as the ventral tegmental area and the substantia nigra (VTA/SN) in response to drug-related cues and impaired sensitivity in these regions to non-drug rewards such as external monetary or social reward cues. The ability to gain self-control of reward-related brain regions through non-drug reward imagery may be impaired in individuals with more severe obsessive and compulsive thoughts about cocaine use. As a result, the severity of obsessive-compulsive thoughts is inversely related to VTA/SN activation during mental imagery. [17]

3. The glucocorticoid-related stress response system

Stressful situations can cause a relapse in a dependent or abstinent person, resulting in the resumption of drug-seeking behaviour. Indeed, it has been proposed that activating the brain stress system causes glucocorticoid release, which affects dopaminergic pathways. Furthermore, the noradrenergic system innervates the extrahypothalamic BSS via the nucleus tractussolitarius (NTS), resulting in a feedforward loop between the corticotropin-releasing factor (CRF) and noradrenaline (NA), which is important in drug addiction and relapse. Glucocorticoids interact with two receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which bind to a GRE site in tyrosine hydroxylase (TH), increasing TH synthaesis and, ultimately, dopamine (DA) release in the nucleus accumbens. PKA and PKC also regulate the cAMP response element binding protein (CREB). The results obtained after pretreatment of morphine-withdrawn rats with mifepristone and spironolactone (GR and MR antagonists, respectively) indicate that glucocorticoids play an important role in addiction because GR would activate ERK and CREB in the NTS, phosphorylating serine 31 and activating TH and, indeed, noradrenergic release in the paraventricular nucleus (PVN).[18]

Conclusion and Future Direction

Understanding the role of the CRF systems in addiction not only provides insight into the neurobiology of the dark side of addiction, but also provides novel targets for identifying vulnerability to addiction and the treatment of addiction. The computational role of DA in the brain through synaptic plasticity and its involvement in several neuropsychiatric disorders, which may shed light on the complicated task of DA in the nervous system. 5-HT2C receptor agonists could be further tested as a potential treatment for psychostimulant addiction. Antagonizing α1 adrenergic receptor signaling has yielded promising results in both, and clinical settings for substance use disorders. The recurring activation of NE transmission in the BNST contributes to the alteration of the function that BNST assumes in how the behavioural response to stress manifests, favoring the establishment of the stress-induced drug seeking. the important role of Prodynorphin polymorphism in Heroin dependence and may guide future studies to identify

genetic risk factors for Heroin dependence. The glutamatergic system as a promising target for the development of novel pharmacotherapies, and in addition, as a potential biomarker for a personalized medicine approach in addiction. These results suggest that OT may be useful in the attenuation of craving, withdrawal symptom in heroin-dependent patients and might be considered a new potential treatment for heroin dependence where positive effects of OT on stress-related hormones may be involved in this effect of OT. The severity of obsessive-compulsive thoughts is inversely related to VTA/SN activation during mental imagery. glucocorticoids have a prominent role in addiction because GR would activate ERK and CREB in the NTS, phosphorylating serine 31 and activating TH and indeed noradrenergic release in the paraventricular nucleus (PVN). These are the major future goals to treat the addiction successfully.

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