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Review

The Role of the Cerebellum in Drug Reward: A Review

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Abstract

Drug abuse remains a global problem; nonetheless, its mechanism has not yet been fully understood. Recent studies have reported on the non-motor functions of the cerebellum, and evidence from neuroimaging and behavioral studies has suggested the role of cerebellum in drug reward, which has received increasing attention. Furthermore, emerging technological developments have aided in clarifying the various circuits and functions of the cerebellum. Exploring the role of the cerebellum in drug reward can improve our understanding of the mechanism underlying addiction and facilitate the development of new treatment schemes. This review summarizes the anatomy of the cerebellum and its connections to brain regions considered important in addiction. Subsequently, we investigate the neurological reasons elucidating why the cerebellum is a potential target for drug reward. Additionally, we expound the molecular targets of addictive drugs in the cerebellum, mainly glutamate and endocannabinoids. Unlike previous studies, this article focuses on the influence of alcohol, nicotine, morphine, cannabis, and cocaine on the cerebellum from multiple viewpoints, including imaging and behavioral changes, molecular signals, neurotransmitters, and synaptic transmission. We aim to clarify some drug-induced cerebellar changes to supplement the previous research regarding the relationship between addiction and the cerebellum. Finally, we discuss the limitations and prospects of drug reward research on the cerebellum to provide novel insights into studying the cerebellum and its role in addiction. We recommend that future addiction network models should include the cerebellum to provide new therapeutic targets for treating addiction.

Keywords: cerebellum; drug reward; morphine; alcohol; nicotine; cannabis; cocaine; addiction

1. Introduction

Seeking positive rewards and avoiding negative punishments is a universal behavior across species. Rewards not only produce pleasure and drive but also reinforce behavior [1]. Investigating the mechanism underlying drug addiction is valuable for understanding reward mechanisms better, given that several clarifications regarding the structure and function of reward circuits were initially made in the context of drug abuse [2]. Drug consumption is driven by reward effects and influenced by genetic, developmental, and psychosocial factors [3]. Addictive drugs disrupt and rewire the circuits of neural substrates related to reward, executive control, and emotion regulation. Thus, drug rewards are characterized by two features: (i) the experience of drug addiction represents the amplification of drug reward effects and the reduction of non-drug rewards effects, and (ii) this drug-induced progressive increase in reward (sensitization) enhances the Pavlovian memory. Simultaneously, the satisfaction derived from actual drug intake gradually diminishes, resulting in tolerance. Subsequently, negative emotions such as anxiety and depression are experienced, leading to a vicious cycle of compulsive drug use to bridge the growing gap between expectations and reality. This harmful reward memory persists and is difficult to forget, resulting in relapse upon withdrawal as well as withdrawal syndrome.

With the development of science and technology, various addictive drugs with potent stimulating effects that far exceed those of drugs directly extracted from natural plants (e.g., opium) have been continuously produced, which has caused serious health and social problems. In 2016, drug abuse claimed the lives of more than 63,300 Americans [4]. The shift in drug-seeking behavior from prescription drugs to illicit opioids has contributed to the rapid increase in drug-related mortality [5]. In addition to death, drug abuse poses potential harm. For instance, drug injection promotes the spread of acquired immunodeficiency disease syndrome [6], and maternal alcohol abuse during pregnancy causes fetal alcohol spectrum disorder, which is characterized by neurocognitive deficits and behavioral abnormalities [7]. Furthermore, drug abuse poses a threat to the lives and health of individuals and imposes immense economic burden. Therefore, studying the mechanism of drug addiction and developing effective therapies are both essential.

Dopamine (DA) plays a central role in various drug rewards [8,9]. Drug addiction is a complex psychiatric disorder involving the interaction of multiple brain regions. The mechanism of drug addiction involves drug-induced lasting molecular and structural plastic changes in the corticostriatal-limbic circuit [10–12]. DA-rich reward-related areas, such as the amygdala and hippocampus, have been extensively studied for drug addiction [13,14]. In contrast, the cerebellum, which is traditionally regarded as a motor brain region, has been neglected in drug addiction

studies because it contains less amount of DA than the aforementioned brain regions. Nevertheless, recent studies have revealed that the cerebellum is involved in various cognitive functions, including emotional memory [15–19], sexual behavior [20,21], language [22], planning [23], and prediction [24,25]; many of these functions are altered in patients with drug addiction. Additionally, neuroimaging studies have provided further evidence supporting cerebellar involvement in drug addiction. For example, a voxel-based morphometry study observed a decrease in the gray matter of cerebellar lobule VI, crus I, and crus II in cocaine abusers [26], whereas a magnetic resonance imaging (MRI) study revealed a considerable reduction in cerebellar white matter volume in nicotine abusers [27]. A functional MRI (fMRI) study also reported functional impairment of the frontostriatal-cerebellar circuit in heroin addicts [28].

While existing research on addiction has provided strong evidence, only few studies have specifically explored the effects of addictive drugs on the cerebellum and related mechanisms. Moreover, specific cerebellar mechanisms and their role in addiction remain unclear. In this review, we focus our discussion on alcohol, nicotine, morphine, cannabis, and cocaine and elucidate how these five drugs affect the cerebellum, including brain imaging and behavioral changes. To explain these mechanisms, we attempt to further explore the changes in molecular signals and neurotransmitters, as well as their synaptic transmission. This will provide some ideas for the study of cerebellum and drug addiction and will also supplement previous research in this field.

2. Functional Anatomy of the Cerebellum

Drug reward research has focused on brain-related circuits; however, the structure of the cerebellum should also be considered. The cerebral cortex and cerebellum account for 81% and 10% of the total brain mass, respectively; however, the total number of neurons in these structures is reversed. According to Lent *et al*. [29], the number of neurons in the cerebral cortex and cerebellum accounts for approximately 19% and 80% of the total number of neurons in the brain, respectively. From the perspective of structure-dependent function, this striking difference suggests that cerebellar functional studies have great potential.

The cerebellum is a bilaterally symmetrical structure located in the posterior cranial fossa and is divided into the middle vermis and bilateral cerebellar hemispheres, which are connected by the vermis [30]. The cerebellar surface contains a richly folded cortex and a deep portion of the medulla. Moulton's analogy of the curled leaves and inner stem of cauliflower helps us to more vividly understand the structure of the cerebellum [31]. The arrangement of fissures on the cerebellar surface identifies 10 distinct lobules in the cerebellar cortex [30], with each lobule being associated with a specific functional cerebral-cerebellar circuit. The functional units of the cerebellar cortex are defined as microregions comprising cortical nuclei and their projections to subcortical structures [32]. The reorganization of these microdomains may be a mechanism of addictive drugs. Neurons in the cerebellum are distributed in the gray and white matter of the deep cerebellar nucleus (DCN); the DCN comprises the fastigial, globular, embolus, and dentate nuclei. The gray matter is divided into the following three layers: (i) the surface layer (also called the molecular layer), which contains the dendrites of Purkinje cells (PCs) and inhibitory interneurons, such as basket and stellate cells; (ii) the intermediate layer (also called Purkinje's layer), which contains the cell bodies of PCs; and (iii) the innermost layer (also called the granular layer), which contains the bodies of granule cells (GCs) and Golgi cells. GCs are the most numerous and only excitatory glutamatergic neurons in the cerebellum, whereas the other four types are γ-aminobutyric acid (GABA)-inhibitory neurons [33]. Climbing and mossy fibers are major inputs to the cerebellum, producing excitatory glutamate neurotransmitters [33]. Climbing fibers originate from the inferior olivary nucleus of the brainstem and form one-on-one synaptic connections to the PCs [34]. Mossy fibers are axons of neurons originating from the cerebral cortex, vestibular nucleus, and spinal cord and terminating in the GC layer of the cerebellum. GC dendrites receive excitatory and inhibitory inputs from mossy fibers and Golgi cell axons, respectively. The GCs emit axons called parallel fibers that project to the PCs to form excitatory synapses for signal transmission [35]. Thus, GABAergic PCs are the only output neurons in the cerebellar cortex that project further to the DCN [30]. The output of the DCN terminates in the motor and non-motor areas of the cerebral cortex, further suggesting the role of the cerebellum in higher cognitive functions.

GABAergic and glutamatergic systems are dominant in the cerebellum. The PCs are the only output neurons in the cerebellar cortex, and the output from the PCs to the DCN is probably a key step for addictive drugs to affect the cerebellum. The mossy fiber GC Golgi cell (MGG synaptic site) and GC parallel fiber PC (GPP synaptic site) are the two key sites in the cerebellar cortex that directly affect the input and output functions of the cerebellum, respectively. Addictive drugs can affect synaptic transmission, including MGG and GPP sites, ultimately affecting PC activity (Fig. 1). Activation of PCs reduces the excitatory output of the DCN because it is a GABAergic neuron, leading to cerebellar dysfunction. In contrast, inhibition of PCs increases the excitatory output of the DCN, thereby alleviating cerebellar dysfunction.

3. Connection Between the Cerebellum and Reward Circuit

Various regions of the cerebellar cortex differ; however, such differences are negligible, as compared to the highly stereotyped arrangement of the cerebellar cortex [36]. One study found uniform interactions within all con-

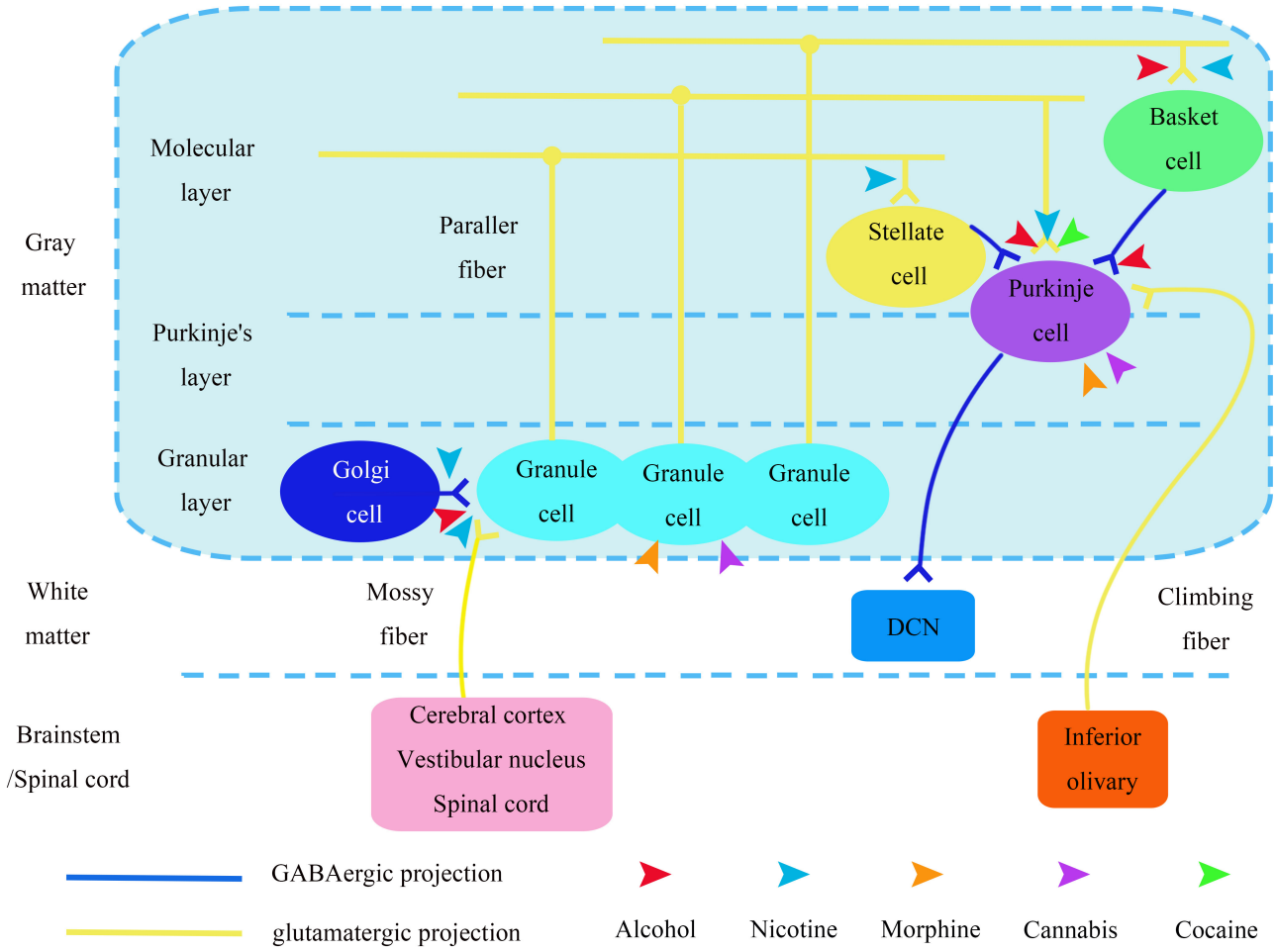

Fig. 1. Drug action sites in the cerebellum. DCN, deep cerebellar nucleus; GABA, γ-aminobutyric acid.

necting networks between the cerebellum and cerebral cortex [37]. Nonetheless, external inputs influence regional differentiation in cerebellar cortical function [36]. According to the cerebellar network theory, interactions between the cerebellum and cerebral cortex may provide the neural basis for cerebellar involvement in cue-induced cravings and addictions [10]. The interconnections between the cerebellum and the rest of the brain are also crucial for understanding cerebellar functions. Therefore, the connection between the cerebellum and drug reward-related brain areas must be explored to further understand the unknown role of the cerebellum in drug reward. Addiction is related to drug-induced plastic changes in the corticostriatal-limbic circuit, and anatomical and functional connections between the corticostriatal-limbic circuit and cerebellum have been reported [10–12]. Therefore, we selected several brain regions that are important for motivation and learning, including the ventral tegmental area (VTA), prefrontal cortex (PFC), basal ganglia, amygdala, hippocampus, and locus coeruleus (LC), to explore the cerebellum's position in the drug reward circuit [12,38–42].

The VTA of the midbrain is the primary source of DA neurons in the brain and can be activated by addictive drugs to release DA in the nucleus accumbens (NAc). Several studies have demonstrated the role of the functional connection between the VTA and cerebellum in drug reward. For example, the functional coupling between the VTA and cerebellum is relatively increased when obese patients are rewarded with high-energy food [43]. After years of exploration, the connection between the VTA and cerebellum has been discovered as mutual. The cerebellum can also receive DA projections from the VTA, mainly in the granular and Purkinje layers [44,45]. Detectable DA levels have been found in the cerebellar vermis and other parts [46]. In addition, the cerebellum projects to the VTA via two independent indirect pathways: the reticulotegmental and pedunculopontine nuclei and the dorsomedial and ventrolateral thalamus [47,48]. The extensive application of various techniques has led to the discovery of connections between various circuits, including the direct pathway from the cerebellum to the VTA. In 2015, Beier *et al.* [49] demonstrated a single synaptic connection from the DCN to the VTA using viral genetic tracing. In 2019, Carta *et al.* [50] optogenetically activated a direct excitatory pathway from the cerebellum to the VTA and reported that this monosynaptic pathway was glutamatergic.

The PFC has been implicated in addiction-related cognitive functions such as executive control, emotion control, and craving. Functional imaging studies in different species have demonstrated a functional connection between the cerebellum and PFC [51–53]. Electrical stimulation of the vermis elicits local field potentials in the medial PFC (mPFC) [54]. Recent studies have identified two indirect pathways through which the cerebellum regulates the PFC, which overlap with the two indirect pathways from the cerebellum to the VTA. The cerebellar dentate or lateral nucleus projects to the reticulotegmental nucleus, which, in turn, projects to the pedunculopontine nucleus, connecting the cerebellum to the PFC [47]. The cerebellar dentate nucleus sends projections to the cortex via the dorsomedial and ventrolateral thalamus [48].

The basal ganglia and cerebellum are the main subcortical structures that influence movement and cognition [11]. In pathological gambling, an addictive disorder, the right ventral striatum has increased connectivity to the right superior gyrus, middle frontal gyrus, and left cerebellum [55]. The NAc is central to the reward circuit, and the striatum is involved in reward, both of which are part of the basal ganglia. Projections from the cerebellum to the striatum via a disynaptic pathway have also been reported [12]. In a study of NAc projections, one pathway to the cerebellum-basal ganglia may be from the DCN to the NAc via the VTA [56]. In monkeys, many synapses from the basal ganglia of the subthalamic nucleus project to the cerebellar cortex through the retrograde transmission of the rabies virus [11]. These results suggest a bidirectional communication between the basal ganglia and cerebellum.

The hippocampus and amygdala have emotional and memory-related functions, they also have connections to the cerebellum [3]. Stimulation of the fastigial nucleus elicits neuronal activity in the amygdala and hippocampus [57, 58]. In patients with major depression, functional connectivity between the cerebellum, amygdala, and hippocampus is altered [59]. Prisoners show increased functional connectivity between the cerebellum and amygdala [60], whereas patients with prescription opioid dependency have decreased functional connectivity between the cerebellum and amygdala [42]. Recently, viral vector-based circuit tracing techniques have discovered disynaptic and trisynaptic connections from the cerebellum to the hippocampus, and the detailed pathways have been previously described [61,62]. In addition, cerebellar microcircuits form functional networks with the septum-hippocampal complex and amygdala via the thalamus [15,63].

The noradrenergic system has been implicated in drug-induced neural plasticity. The LC is one of the major sources of norepinephrine in the brain and plays an important role in cognitive function [64,65]. Cerebellar DCN neurons and PCs are directly connected to the LC, and axonal projections from the PC innervate the noradrenergic neurons in the LC [66,67].

All of these brain regions play different roles in drug addiction, and the cerebellum has anatomical or functional connections to all of them, suggesting that the cerebellum should be considered as a new direction in drug addiction research. We have discussed the addiction-related network by summarizing the connection between the cerebellum and other brain regions (Fig. 2 Ref. [12,15,44,45,47–50,56,61–63,66,67]). We anticipate that future addiction network models will include the cerebellum. In addition, external inputs determine the regional differentiation of cerebellar cortical function; however, cerebellar outputs are realized through PC projections to the DCN. The DCN comprises four parts—namely, the apical, globose, embolus, and dentate nuclei. Therefore, further studies on the output of specific cerebellar subregions should be conducted to better understand the function of the cerebellum.

4. Molecular Substrates Involved in Drug Reward in the Cerebellum

The neural basis of drug reward is the change in synaptic plasticity caused by drug action on addiction-related circuits [39,68]. The cerebellum contains many molecular targets involved in drug-induced neuroplasticity. Drugs of abuse can act on these targets to alter synaptic structure and function, thus reorganizing the corticostriatal-limbic circuit and generating addiction-related behavioral phenotypes. DA is central to various drug reward systems [8,9], and neuroplasticity induced by various addictive drugs is related to the role of DA. As previously mentioned, the cerebellar vermis can receive DA energy projection from the VTA [44,45], and detectable DA levels have been found in the vermis [46]. However, the DA content in the cerebellum is relatively low, and non-DA systems should be focused on in cerebellar neuroplasticity. The cerebellar effects of specific drugs in the next section also involve other systems, such as the glutamatergic, endocannabinoid, GABAergic, norepinephrine, and serotonin systems. In a 2009 review, Miquel mentioned that short- and long-term plasticity of cerebellar synapses are mediated by glutamate- and endocannabinoid-dependent cellular mechanisms [69]. The glutamatergic system mainly involves the release of glutamate and the structural and functional changes in glutamate receptors such as N-methyl-d-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid hydrate (AMPA), and metabotropic glutamate receptors, which are related to synaptic plasticity. The endocannabinoid system can modulate the rewarding properties of non-cannabinoids [70,71]. The endocannabinoid system consists of endocannabinoids and their homologous receptors cannabinoid type 1 receptor (CB1R) and cannabinoid type 2 receptor (CB2R), which induce neural plasticity and participate in drug addiction [72]. The cerebellum contains a high density of cannabinoid receptors, particularly the CB1 receptor [73], which can modulate synaptic plasticity in the cerebellar cortex

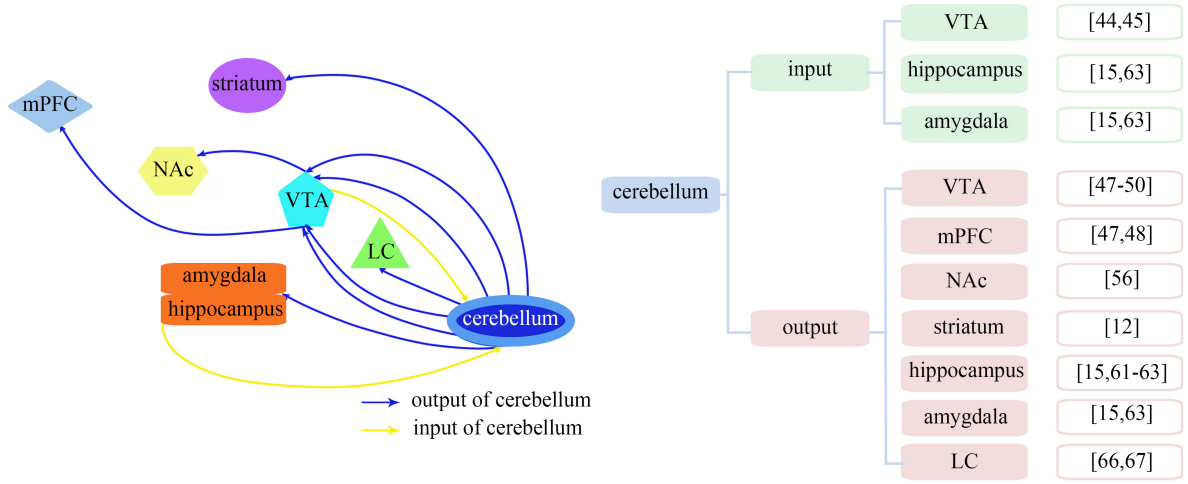

Fig. 2. Schematic of the connection between the cerebellum and reward circuit. NAc, nucleus accumbens; mPFC, medial prefrontal cortex; VTA, ventral tegmental area; LC, locus coeruleus.

[74]. For example, the CB1 receptor and G protein function in the cerebellum of individuals with alcohol use disorders (AUD) are reduced [75]. The endogenous opioid system modulates the mesolimbic DA system and often interacts with the endocannabinoid and endogenous opioid systems to promote reward-motivated behavior [76,77]. In addition to the above neurotransmitter changes that highlight plasticity, perineural nets (PNNs) also contain proteins that alter synaptic plasticity and may be involved in maladaptive learning associated with addiction. Activity in cerebellar PNNs is also altered by cocaine-related memory induction [78].

Neuroadaptation resulting from the interaction between the DA and glutamatergic systems and the upregulation of several intracellular pathways are also the basis for increased sensitivity to the behavioral effects induced by addictive drugs. Behavioral sensitization refers to the gradual increase in the behavioral response to a drug that develops during repeated dosing and persists over a long period [79,80]. Pavlovian conditioned memory plays an important role in drug reward, and drug sensitization strengthens the link between cue and reward in Pavlovian conditioned memory. In addition, glutamate-endocannabinoid synaptic interactions in the cerebellum have also been implicated in cocaine-induced sensitization [81].

Thus, the interaction between the DA, glutamate, and endocannabinoid systems mediates drug-induced prominent plasticity in the cerebellum that can lead to behavioral sensitization. The DA in the cerebellum mainly comes from other brain regions, such as the dopaminergic projection of the VTA, suggesting that the role of the DA system in the cerebellum is not as prominent as that in other brain regions. This view is also supported by the following description of the interaction of various substances with the cerebellum. Thus, the cerebellum can participate in drug reward because of its molecular targets suitable for drug addiction.

5. Common Addictive Drugs and the Cerebellum

5.1 Alcohol

Alcohol consumption is a world-class cultural phenomenon, with AUD affecting millions worldwide and causing huge economic and social costs [82]. The rewarding effects of alcohol are the main reasons for alcohol abuse, and they have transient or irreversible consequences on the nervous system, including motor, cognitive or social impairment [83]. Acute alcoholism and chronic alcohol dependence are major factors associated with illness, injury, and death in healthy populations [84]. Fetal alcohol spectrum disorder is the leading cause of mental retardation in Western countries and affects approximately 1% of newborns [85].

The cerebellum is the brain region most affected by alcohol consumption, suggesting its potential role in alcohol addiction. Neuropathological examination and imaging, such as MRI, have confirmed that adult alcohol dependence leads to cerebellar volume reduction and selective damage to the anterior superior cerebellar lobule and white matter regions in patients with AUD [86]. A prospective study of adolescents discovered that drinking groups, compared with non-drinking or low-drinking groups, demonstrated accelerated gray matter loss in the anterior lobule and vermis, which are common areas of the effect of chronic alcoholism [86]. Immature neurons in the cerebellum are more sensitive to alcohol than mature neurons during growth and development. Prenatal exposure to alcohol causes permanent motor and cognition-related deficits, which are the effects of alcohol on the developing cerebellum. MRI studies have shown that children and adolescents with a history of prenatal alcohol exposure have decreased cerebellar volume and reduced vermis size. An experimental animal study suggested that cerebellar volume reduction was

mainly due to the loss of PCs and GCs [87]. In addition, alcohol could induce glial cell apoptosis in the cerebellar white matter [88].

Alcohol-induced cerebellar dysfunction has been shown by previous studies to be mainly caused by the destruction of the MGG and GPP synaptic sites [89]. GCs receive excitatory glutamatergic input from mossy fibers in the cerebral cortex, vestibular nucleus, and spinal cord, making them the main input sites in the cerebellum. The GCs also receive inhibitory GABAergic inputs from Golgi cells. Nitric oxide synthase (NOS) is widely distributed in the cerebellar cortex, except in the PCs [90,91]. Alcohol activates Golgi cells by inhibiting NOS in the cerebellum, causing a decrease in nitric oxide (NO) content [92]. In addition, ethanol directly potentiates the extra-synaptic $GABA_A$ receptors on the GCs. These all lead to a decrease in GC activity. Excitatory afferent inputs from mossy fibers to the GCs are inhibited, resulting in cerebellar shorting. Additionally, the GCs can project to inhibitory interneurons (such as basket and stellate cells) and form feedforward control over the PCs. Decreased GC activity also resulted in decreased glutamate transmission from parallel fibers to the PCs and inhibitory interneurons. This process only occurs at the MGG synaptic site, as PCs do not contain NOs. Alcohol also inhibits the ethanol-specific nucleoside transporter (ENT 1), increasing the adenosine content in the cerebellum [93,94]. The A1 adenosine receptor (A1 AR) is found in GCs, parallel fibers, and basket cells, but not in stellate cells [95–97]. Therefore, high concentrations of adenosine acting on the A1 AR cause synaptic inhibition, including GPP synaptic site and excitatory glutamatergic synaptic transmission between parallel fibers and basket cells, and inhibitory GABAergic synaptic transmission between basket cells and PCs [98]. The synergistic effect of these processes ultimately leads to an abnormal activation of cerebellar PCs and a reduction in the excitatory output of the DCN. In addition, chronic and acute ethanol use alters CB1 receptor expression, density, and function. The CB1 receptor and G protein function in the cerebellum are reduced in individuals with AUD [75].

Alcohol affects the cerebellum and causes changes in the MGG and GPP synaptic sites and synaptic connections between parallel fibers and basket-like filaments, mainly mediated by NO and adenosine. Activation of Golgi cells by NO results in an increase in GABA content in MGG and a decrease in glutamate transmission in parallel fibers. Adenosine causes a decrease in glutamate release from GPP and parallel fibers to inter-synaptic basket-shaped cells. Inhibiting GC input function and over-activating PCs responsible for output mediate alcohol-induced cerebellar inhibitory dysfunction. Moreover, the key MGG synaptic site and GABA projection between inhibitory interneurons and PC synapses are both $GABA_A$ receptor-mediated [99], suggesting the role of $GABA_A$ receptors in the ethanol effect on the cerebellum.

5.2 Nicotine

Smoking is a public health issue worldwide and is estimated to cause 8 million deaths annually by 2030 [100]. Nicotine, the main addictive substance in cigarettes, is the second leading cause of death worldwide [101]. Relapse rates for smoking cessation remain high despite strong subjective will and first-line therapies.

Extensive evidence supports the effects of nicotine on cerebellar structure and function. MRI studies have reported that smokers have reduced gray matter integrity in several brain regions, including the cerebellum [102]. The gray matter volume of the left Crus I is inversely correlated with nicotine dependence severity assessed by the Fagerström Test for Nicotine Dependence [103]. The excitotoxic effects of nicotine can lead to apoptosis of cerebellar neurons, especially the PCs and GCs [104,105]. The developing cerebellum of different species supports this view. For example, maternal smoking during pregnancy directly reduces the size of the cerebellum in utero [106]. Long-acting nicotine exposure significantly affects the histogenesis of the cerebellar cortex in chick embryos during incubation [107]. Furthermore, studies utilizing resting-state fMRI have reported increased spontaneous activity and functional connectivity in the anterior cerebellar lobe in smokers and increased functional connectivity in the right dorsolateral PFC, left middle temporal gyrus, and anterior cerebellar lobe in relapse after withdrawal [108–110]. Abnormalities in cortical-cerebellar and cerebello-striatal functional connectivity have also been observed in smokers and are suggested to be associated with nicotine dependence [101,103]. Some studies have demonstrated that cerebellar functional connectivity can accurately predict smoking recurrence [110].

Positron emission tomography studies have revealed that repeated nicotine exposure in smokers upregulates the density of nicotinic acetylcholine receptors (nAChR). This increase in density suggests a decrease in the likelihood of quitting smoking [111]. Prenatal nicotine exposure impairs the nutritional effects of acetylcholine by binding prematurely to nAChRs [112]. These results indicate that nAChR is the main site of the pharmacological action of nicotine in the central nervous system. The cerebellum contains $\alpha 7$ and $\alpha 4\beta 2$ receptor subtypes, which are sensitive to nicotine-induced sensitization [103]. Nicotine regulates sensory information processing in the cerebellar GC layer via $\alpha 7$ and $\alpha 4\beta 2$ subunit receptors [113] and increases glutamatergic and GABAergic transmission in the cerebellum by binding to nAChRs. However, desensitization of nAChRs occurs, and GABAergic neurons are more sensitive to this than glutamatergic neurons [114]. Thus, nicotine-induced glutamate transmission via nAChR is superior to GABAergic transmission. Chronic nicotine treatment results in increased glucose oxidation and neurotransmitter circulation associated with glutamate neurons

in brain regions outside the cerebral cortex [115]. Thus, the net effect of long-term nicotine exposure is an increase in excitatory glutamatergic transmission in the cerebellum, thereby favoring the activation of dopaminergic neurons in other reward-related circuits, such as the VTA and NAc. Functional antagonism occurs between nicotine and alcohol, and the cerebellum plays an important role. For example, the $\alpha 7$ and $\alpha 4\beta 2$ subtypes of nAChR are potential sites for functional antagonism, as both subtypes reduce alcohol-induced cerebellar ataxia [116]. As previously described, the inhibitory dysfunction of the cerebellum is due to alcohol use, whereas nicotine mainly causes excitatory dysfunction in the cerebellum. This is consistent with an increase in glutamatergic transmission in the cerebellum caused by nicotine action on nAChRs.

Studies have demonstrated that long-term nicotine use enhances excitatory activity in multiple brain regions outside the cerebral cortex [115]. The different effects on NO content may be one of the reasons for their functional antagonism. Unlike ethanol, which reduces cerebellar NO content by inhibiting NOS, nicotine can promote NOS to increase NO content by activating cerebellar nAChR and releasing endogenous glutamate [90,117,118]. The increase in NO content can prevent the inhibition of the GCs by Golgi cell activation, thus preventing the conduction block of mossy fibers to the GCs. Glutamate release from the MGG and GPP synaptic sites and the synapse from the parallel fibers to the inhibitory interneuron also increases. NO can also stimulate guanylyl cyclase, increase cyclic guanine monophosphate (cGMP) production, and inhibit PC discharge [90,119]. The result of these processes is an increase in cerebellar excitability. In addition, activating nAChR regulates norepinephrine release during cerebellar development [120].

Thus, nicotine affects the cerebellum by acting on nAChRs, particularly the $\alpha 7$ and $\alpha 4\beta 2$ isoforms. The net result of nicotine action on the cerebellum is an increase in excitatory glutamatergic transmission, whether the neurotransmitter changes are caused by the direct action of nicotine on nAChRs or are mediated by NO. Conversely, the net effect of alcohol on the cerebellum is inhibitory dysfunction. The opposite effects of nicotine and alcohol on cerebellar function suggest that the cerebellum plays a diverse role in drug reward.

5.3 Morphine

Opioid abuse is a global problem, and morphine, the most effective analgesic among opioids, is addictive [121]. Morphine is one of the main active ingredients of opium poppy and primarily acts by binding to μ-opioid receptors (MOR) [122]. Absolute quantitative real-time reverse transcriptase polymerase chain reaction studies revealed that MOR mRNA is at high levels in the cerebellum, whereas κ-opioid receptor mRNA and δ-opioid receptor mRNA are at relatively low levels [123]. Morphine and its metabolites can also be found in the cerebellum, suggesting that morphine is closely related to the cerebellum [124,125].

Fetal size and head circumference are reduced in children prenatally exposed to opioids [126]. In utero, morphine exposure reduces the number and volume of PCs in the cerebellum of developing pups [127]. Preterm morphine exposure is independently associated with impaired cerebellar growth during the neonatal period [122,128]. In albino rats, oral administration of 5 mg/kg body weight morphine daily for 30 days resulted in vacuolation of the cerebellum's molecular layer, reduction in the number and volume of PCs, and degeneration of granulosa cells [129].

Morphine induces more diverse changes in the molecular and neurotransmitter systems of the cerebellum than alcohol and nicotine. Morphine exposure can induce abnormal calcium signaling in the cerebellum; in particular, acute and chronic morphine exposure can decrease the calbindin levels, increasing cerebellar fragility [130,131]. Furthermore, morphine reduces the availability of calcium channels that regulate the output of the cerebellar cortex [132,133] and increases NOS activity in the cerebellum [134]. The mechanism by which higher NO levels cause increased excitatory transmission in the cerebellum has been described in the nicotine section as an increase in excitatory glutamate transmission and an increase in cGMP levels. Sustained morphine exposure reduces the availability of GABA receptors in the cerebellum [135]. Acute opioid administration to the cerebellum decreases electrically stimulated norepinephrine release, and chronic morphine exposure decreases the cerebellar norepinephrine levels [129,136]. Studies investigating the effects of morphine on the cerebellar glutamatergic system have focused on glutamate receptors, particularly NMDA receptors [137]. Prenatal opioid exposure leads to an increase in NMDA receptor-induced calcium influx into the cerebellum of chick embryos and a decrease in the expression of the GluN2B subunit of NMDA receptors in the cerebellum of rats after birth [127].

CB1 receptors in the endocannabinoid system are also involved in the effects of morphine on the cerebellum [138]. However, how morphine affects NMDA and CB1 receptors to change cerebellar function remains unclear. Acute morphine injection resulted in a decrease in cerebellar serotonin levels, whereas oral administration of 5 mg/kg body weight morphine for 10 and 30 days resulted in an increase in cerebellar 5-hydroxytryptamine (5-HT) levels in albino rats [139]. This suggests that the effects of morphine on the cerebellum may be related to the mode, dose, and frequency of administration, suggesting the complex effects of opioids, such as morphine, on the cerebellum. In addition, repeated administration reduces cerebellar dynorphin and Met-enkephalin levels, endogenous opioid ligands that modulate reinforcement and relapse-related behaviors of different drugs [140,141].

The effects of morphine have been extensively studied compared with alcohol and nicotine. Morphine causes changes in molecular and neurotransmitter systems in the cerebellum, including decreased availability of GABA receptors, increased glutamate transmission, and altered calcium signaling. The specific changes induced by morphine require further study; however, the comprehensive analysis suggests that the effects of morphine and nicotine on the cerebellum are similar. They all ultimately manifest as increased cerebellar excitatory transmission.

5.4 Cannabis

Cannabis is one of the most commonly used addictive drugs worldwide [142]. Over and above the recent increase in the number of countries and regions supporting the legalization of cannabis, cannabis is more widely used in medical treatment and recreational settings [143,144]. Non-medical cannabis usage may be linked to an increased risk of anxiety and depression, and cannabis has also been indicated to prompt other mental diseases [145]. Cannabis can be fatal if it facilitates various adverse cardiovascular reactions [146].

Delta-9-tetrahydrocannabinol (THC) and cannabidiol represent the two primary active substances in cannabis, with THC being more widely studied than cannabidiol [147]. These substances have a wide range of uses, including as a pain reliever after chemotherapy or antipsychotic; nevertheless, they are addictive, especially THC, which is a partial CB1R and CB2R agonist [145]. CB1R, a well-researched receptor widely distributed in the cerebellum, cortex, hippocampus, and other parts of the central nervous system, is closely associated with drug addiction [148] and displays a high expression in the molecular layer of cerebellar parallel fiber ends [149]. The combination of THC and CB1R can modulate retrograde endocannabinoid signal, resulting in a broad range of neurotransmitter activities, including the modulation of glutamate and GABA release, as well as complex interactions with dopaminergic, serotonergic, noradrenergic, and endogenous opioid systems [150–154]. While mainly located in the immune system, CB2R is also found in the microglia and plays a main role in the immune system and central nervous system [155–157]. Interestingly, CB2R is upregulated in microglial activation and, in turn, is expressed at low or undetectable levels when the microglia are under resting homeostatic conditions [158].

A growing body of research indicates that the cerebellum may be linked to cannabis addiction. Blithikioti *et al.* [150] examined cerebellar changes in cannabis users and reported that the users displayed increased cerebellar gray matter volume and changes in the cerebellar resting state after long-term use and that cerebellum-dependent functions, such as memory, decision-making, and ability to overcome associative learning obstacles, were affected [150]. A recent study detected hyperconnectivity in resting networks among cannabis users [159]. When specifically looking at decision-making activity, independent component/connectivity analysis revealed significantly increased functional coupling between the anterior cerebellum region IX and the right nucleus accumbens, left pallidum, and left putamen; additionally, the volume of the left nucleus accumbens significantly increased [159]. This hyperconnectivity in resting networks may be associated with the difficulty in quitting and frequent relapse among cannabis users, and the enhanced connection between the cerebellum and NAc may lead to a higher desire for the drug [160]. This highlights the role played by the NAc in the process of interaction between cannabis and the cerebellum.

However, the results of a study on multiple sets of twins with shared genetic or environmental factors confound these findings. By using the resting-state fMRI technique to examine twins who were disparate cannabis users, this study showed that factors other than cannabis could contribute to alterations in cerebellar-cortical activity [161]. This does not negate the role of the cerebellum in cannabis addiction. In addition to decision-making, visuomotor adaptation is a task mediated by the cerebellum. A case-control study revealed that sensorimotor adaptation was altered in chronic cannabis users, likely because of saturation of the endocannabinoid system after chronic cannabis use [162].

The combined use of cannabis and alcohol activates presynaptic CB1R in the PCs and enhances the synaptic glycine receptor, leading to more intense PC activity than when used alone [163]. Aside from the PCs, cerebellar GC activity and synchronization may be involved in the development of cannabinoid physical dependence because chronic THC administration severely impairs the GC activity and network coordination [164]. Cannabinoid withdrawal induces ataxia, tremor, and abnormal posture; additionally, the number and network correlation of active GCs have been reported to increase [164,165]. However, the cannabis withdrawal mechanism is more linked to cerebellar cyclic adenosine monophosphate (cAMP) pathways. A previous study on THC withdrawal over time indicated the correlation between the cerebellum, adenylate cyclase and downstream protein kinase A activation, and withdrawal symptoms and showed that the application of selective cAMP blockers could significantly reduce THC withdrawal symptoms [166]. Therefore, one can conclude that withdrawal symptoms are caused by activated cAMP pathways. Interestingly, studies have shown that microglia activation may cause a cerebellar defect. The chronic THC exposure activates the cerebellar microglia and increases the expression of IL-1β, a nerve inflammation marker, while CB1R increases in molecular layer and CB2R expression reduced [167]. IL-1β directly regulates PC activity, thereby affecting its projection area function and causing a particular cerebellar function defect [168].

Considerable imaging and behavioral evidence suggests that the cerebellum plays a role in cannabis addiction

Table 1. Themajor cerebellar changes caused by drugsin both human image and preclinical animal studies.

Drugs	Human image and preclinical animal studies	Research object	Reference
Alcohol	cerebellar volume reduction	Human	[86]
	selective damage to the anterior superior cerebellar lobule and white matter regions	Human	[86]
	accelerated gray matter loss in the anterior lobule and vermis	Human	[86]
	decreased cerebellar volume and reduced vermis size	Human	[87]
	induce apoptosis of glial cells in the cerebellar white matter	Rats	[88]
Nicotine	reduced gray matter integrity	Human	[102]
	apoptosis of cerebellar neurons	Rats	[104,105]
	reduces the size of the cerebellum in utero	Human	[106]
	affects the histogenesis of the cerebellar cortex in embryos	Chickens	[107]
	increased spontaneous activity and functional connectivity in the anterior cerebellar lobe	Human	[108–110]
	abnormalities in cortical-cerebellar and cerebello-striatal functional connectivity	Human	[101,103]
Morphine	reduces the number and volume of PCs in the cerebellum of developing pups	Human	[127]
	impaired cerebellar growth in the neonatal period	Human	[122,128]
	vacuolation of the molecular layer of the cerebellum	Rats	[129]
	reduction in the number and volume of PCs	Rats	[129]
	degeneration of granulosa cells	Rats	[129]
Cannabis	increased volume of the cerebellar gray matter	Human	[150]
	increased changes in the cerebellum resting state	Human	[150]
	cerebellum-dependent functions were affected	Human	[150]
	hyper connectivity was demonstrated in resting networks	Human	[159]
	enhanced connection between cerebellum and NAc	Human	[160]
Cocaine	lower gray matter volumes in the bilateral cerebellum	Human	[26,179]

PCs, Purkinje cells; NAc, nucleus accumbens.

by activating the CB1R receptors, which subsequently adjust various neurotransmitters such as glutamate [150–154]. Nonetheless, research clearly demonstrating THC addiction as the cause of brain neurotransmitter system changes remains relatively limited. cAMP blockers in the lateral ventricle have also been shown to not ease withdrawal symptoms, further prompting the specific role of the cerebellum in cannabis addiction [166]. Considering the activation of cerebellar microglia and other nerve-related inflammatory factors, additional exploration of the role of the cerebellum in drug addiction is warranted.

5.5 Cocaine

Cocaine, a crystalline scopolamine extracted from coca bushes, acts as a powerful local anesthetic that can lead to addiction [169]. Cocaine inhibits the reuptake of monoamine transmitters, such as DA, 5-hydroxytryptamine, and norepinephrine [170,171]. The interaction between cocaine and the monoamine neurotransmitter system in the cerebellum has also been shown. Cocaine exposure in newborns causes an increase in cerebellar 5-hydroxytryptamine levels and may lead to motor dysfunction [172]. Additionally, acute and repeated cocaine exposure and withdrawal result in changes in the endogenous cannabinoid system in the mouse cerebellum and are considered to be related to the adaptation after mental stimulant addiction [81,173]. The change in phosphocholine cytidylyltransferase activity, which is also often regarded as related to lipid dysregulation in various nervous system disorders, has also been observed in the cerebellum after cocaine exposure [174]. Cocaine promotes oxidative stress and increases the expression of lysosome mononuclear phagocyte marker ED1 (a lysosomal protein which is overexpressed during inflammatory challenge) in rat cerebellum, which therefore supports the theory of cerebellar involvement in addiction from the perspective of inflammation [175]. From the perspective of imaging, cerebellar gray matter deficits are among the most persistent and substantial brain changes detected in long-term abstinence-dependent individuals [176]. In particular, lobule VIII of the cerebellum has been extensively investigated by studies on the mechanism of cocaine addiction [177,178]. Multiple studies have observed a lower gray matter volume in the bilateral cerebellum among cocaine-dependent individuals and reported a negative correlation between the cerebellar gray matter volume and the duration of cocaine use, as well as deficits in executive function and reduced motor performance [26,179].

Research on the mechanisms underlying cocaine addiction in relation to the cerebellum has focused more on Pavlovian conditioning and drug-cue associative memories, which trigger cocaine addicts to seek and take [180]. Conditioned preference towards an odor associated with cocaine is related to *cFOS* expression in the dorsal region of the

Table 2. The main receptor and neurotransmitter system in which drugs act in the cerebellum.

Drugs	Major receptors in the cerebellum	Neurotransmitter systems in the cerebellum
Alcohol	$GABA_A$ receptors [7]	GABAergic system [7,98] Glutamatergic system [98] Endocannabinoid system [75]
Nicotine	nAChR, especially the α7and α4β2 subtypes [103,111–113]	Glutamatergic system [7,115] Norepinephrine system [120]
Morphine	MOR [122,123]	GABAergic system [135] Norepinephrine system [129,136] Glutamatergic system [7,115,134,137] Endocannabinoid system [138] Serotonin system [129,139] Endogenous opioid peptide system [140,141]
Cannabis	CB1R [148,149]	Endocannabinoid system [150] GABAergic system [151] Glutamatergic system [151] Dopaminergic system [152] Serotonin system [153] Noradrenergic system [153] Endogenous opioid peptide system [154]
Cocaine	Monoamine transporters [170,171]	Dopaminergic system [170,171] Serotonin system [170,171] Norepinephrine system [170,171] Endocannabinoid system [81,173]

GABA, γ-aminobutyric acid; nAChR, nicotinic acetylcholine receptors; MOR, μ-opioid receptors; CB1R, cannabinoid type 1 receptor.

GC layer in the cerebellar vermis [181], and the lobule VIII activity has been shown to be significantly correlated with this conditioned preference [182]. Nevertheless, neurotoxic lesions in lobule VIII can also increase cocaine-induced conditioned preference, and increased *cFOS* expression in the mPFC and striatum has also been found [183]. This prompted Gil-Miravet *et al*. [183] to propose an explanatory model for the cerebellar influence on cocaine-induced conditioned preference: the direct projection from the DCN to the VTA receives the Purkinje axon from lobule VIII. Damage to the cerebellar vermis can lead to the disinhibition of mPFC and striatum subregions, thereby promoting the drug effect of cocaine because these subregions mainly receive DA projections from the VTA [183,184]. A previous study using a model of infralimbic (IL) cortex deactivation also observed cocaine-induced preference after dorsal cerebellar cortex damage; however, the deactivation of the ventral region of lobule VIII and prelimbic cortices did not exhibit similar effects [185]. The simultaneous inactivation of IL and dorsal lobule VIII prevents their respective inactivation and promotes cocaine-induced conditioned preference, suggesting the functional compensation relationship between the two [185]. When the IL or dorsal lobule VIII is damaged, another region plays a greater role in conditioned reflex, as compared when they are not damaged. The simultaneous deactivation of these two regions undermines this compensatory relationship. Therefore, the cerebellum and IL may jointly act on the Pavlovian conditioning of cocaine.

In addition, cocaine-induced conditioned preference memories resulted in the up regulation of Golgi inhibitory interneurons in the cerebellar vermis [186]. PNNs can limit the plasticity of neurons and promote synaptic stability, and are considered to be one of the key mechanisms for maintaining drug-induced long-lasting memories [186–188]. Injury to lobule VIII can increase the expression of PNNs in the lateral nucleus, mPFC and striatum [183]. Inactivation of IL can also up regulate the expression of PNNs around Golgi interneurons [189]. Long term self administration of cocaine exhibits stronger PNNs during withdrawal to dynamically regulate cerebellar plasticity, indicating the stability of drug-induced synaptic changes and explaining why drug-induced memory is so persistent [190]. Using the enzyme chondroitinase ABC to digest PNNs in the lobule at different time points, it can be found that PNNs digestion in the lobule destroys cocaine-induced short-term memory and conditioned preference, and contributes to the recovery of cocaine-induced conditioned preference [191]. Therefore, the up-regulated PNNs around the Golgi interneurons are used to maintain cocaine-induced conditioned preference memories [191].

Other psychostimulants such as amphetamine and methamphetamine have not been widely studied for their

cerebellar effects; however, cocaine- and amphetamine-regulated transcript peptides in climbing fiber-PC synapses in the rat vestibular cerebellum are believed to be related to reward and reinforcement [192]. In summary, the cerebellar characteristics of cocaine-induced preference conditioning include increased activity of dorsal cerebellar GCs and enhanced PNNs around Golgi neurons [193]. These two major changes both involve mPFC and striatum, further emphasizing the importance of incorporating the cerebellum into a part of cortical-striatal-limbic loops for drug addiction research.

We summarize the major cerebellar changes caused by the aforementioned addictive drugs in order to better understand how each drug alters cerebellar function (Table 1, Ref. [26,86–88,101–110,122,127–129,150,159,160,179]). Despite differences in receptor binding and neurotransmitter secretion (Table 2, Ref. [7,75,81,98,103,111–113,115,120,122,123,129,134–141,148–154,170,171,173]), all five drugs ultimately exhibit excitatory or inhibitory dysfunction in the cerebellum. DA did not significantly affect the cerebellum compared to conventional studies of addiction brain area. Glutamate and GABA are the main excitatory and inhibitory neurotransmitters in the central nervous system, respectively. Glutamatergic and GABAergic systems are also ubiquitous in the cerebellum during drug reward. The role of the glutamatergic system in synaptic plasticity and behavioral sensitization has also been described. In addition, while each drug has different specific mechanisms of action, the existence of some commonalities is worthy of further research. For example, the first three drugs all act on cerebellar NOS, indicating the role of NOS in addiction and the sensitivity of addiction therapies targeting NOS.

6. Summary and Prospect

The focus of this review lies in exploring changes in the cerebellum caused by various drugs and drug addiction. Although previous studies have shown that drug addiction may be related to cerebellar emotions and cognition, it is necessary to explore different addiction processes in order to integrate the cerebellum into the addiction circuit, which is also the purpose of our review. Previous evidence of cerebellar involvement in drug addiction has focused on neuroimaging; however, this is insufficient in understanding how the cerebellum plays a role in drug reward. In this review, we highlighted the effects of common addictive drugs, such as alcohol, nicotine, morphine, cannabis and cocaine, in the cerebellum and how they cause changes in many aspects, including molecular signaling and synaptic transmission. Through the above discussion, various drugs may affect the cerebellum by altering its neurotransmitter system. This result is a change in cerebellar function, which affects addiction related circuits and causes behavioral changes. Therefore, further research focuses on the cerebellum and drug addiction lies in the position of the cerebellum in the reward circuit, which needs to further explore the anatomical and functional connections between the cerebellum and other brain regions, as well as the changes in the cerebellar neurotransmitter system caused by drugs.

However, further research is required to support how these changes contribute to the cerebellar role in drug reward. The cerebellum is often viewed in relative isolation, which is more limited, regarding molecular targets and specific changes caused by drugs. For example, we have only described the effect of alcohol on the cerebellar afferent block and the enhancement of inhibitory output without considering how the cerebellum affects the function of other brain regions. We have only reviewed the connections between the cerebellum and a few brain regions of the reward circuit, and further research is needed on how the cerebellum might be further involved in the drug reward circuit. Further refinement of cerebellar inputs to specific subregions should also be verified. As part of the addiction circuit, the cerebellum should work with other brain regions to regulate the complex process of drug addiction. Therefore, the description of the role of cerebellum in drug reward is insufficient, and no addiction network model that includes the cerebellum has been reported. The cerebellum remains a relatively low-ranking brain region in drug addiction research, and the inconsistency among some research data makes its discussion difficult. Nevertheless, we should recognize the importance of including the cerebellum in the addiction network. The mechanism of addiction has not been thoroughly studied, which contributes to the poor effectiveness of addiction treatment. The cerebellum participates in the mechanism of addiction and provides a new target for addiction treatment. For example, we discovered that the effects of alcohol, nicotine, and morphine on the cerebellum involved changes in NO content, suggesting that we can regulate NOS and NO in the cerebellum to treat drug addiction. The specific effects have not been studied; however, this may provide new ideas for addiction treatment that can replace the currently ineffective ones.

Various emerging research techniques, such as optogenetic technology, have enabled the discovery and refinement of cerebellar circuits related to drug reward. Research on food and internet addiction models has also contributed data on how the cerebellum participates in addiction. We hope that this review of changes in the cerebellum caused by addictive drugs will be taken seriously and spark the research required for new targets to treat addiction.

Abbreviations

DA, dopamine; MRI, magnetic resonance imaging; fMRI, functional MRI; DCN, deep cerebellar nucleus; PC, Purkinje cells; GC, granule cells; GABA, γ-aminobutyric acid; MGG synaptic site, mossy fiber GC Golgi cell; GPP synaptic site, GC parallel fiber PC; VTA, ventral tegmental area; PFC, prefrontal cor-

tex; LC, locus coeruleus; NAc, nucleus accumbens; mPFC, medial prefrontal cortex; PMDA, N-methyl-d-aspartate; AMPA, α-amino-3-hydroxy-5methylisoxazole-4-propionic acid hydrate; CB1R, cannabinoid type 1 receptor; CB2R, cannabinoid type 2 receptor; AUD, alcohol use disorders; PNNs, perineural nets; NOS, Nitric oxide synthase; NO, nitric oxide; ENT 1, ethanol-specific nucleoside transporter; A1 AR, A1 adenosine receptor; nAChR, nicotinic acetylcholine receptors; cGMP, cyclic guanine monophosphate; MOR, μ-opioid receptors; THC, delta-9-tetrahydrocannabinol; cAMP, cyclic adenosine monophosphate; IL, infralimbic.

Author Contributions

YL designed the manuscript structure. YB-W designed the figures and conducted a literature review. YL and YB-W exchanged ideas and suggestions throughout the writing process. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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