Review

Neurobiology

Monoamine Neurotransmitters and Drug Addiction

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Drug addiction is a chronic, relapsing brain disease. Various addictive drugs act on the reward circuit and eventually cause changes in the release of neurotransmitters, resulting in a rewarding effect. Among them, the monoamine neurotransmitters 5-hydroxytryptamine, norepinephrine and dopamine play an essential role in drug addiction. The role and mechanism of monoamine neurotransmitters in drug addiction are reviewed and discussed.

Keywords: Drug Addiction; Monoamine Neurotransmitter; Serotonin; Norepinephrine; Dopamine; Reward Circuit

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DRUG addiction is an abnormal compensatory adaptation of neurons to the long-term use of addictive drugs, leading to symptoms such as tolerance, sensitization, dependence, and relapse (1). The mesolimbic reward system is the most important neuroanatomical basis of drug addiction. Various addictive drugs act on the reward circuit and eventually cause changes in the release of neurotransmitters, resulting in a rewarding effect. Neurotransmitters related to drug addiction are mainly monoamine neurotransmitters, including 5-hydroxytryptamine (5-HT) and catecholamine (CA), which includes norepinephrine (NE), epinephrine (E), and dopamine (DA) (2, 3). Therefore, the role of monoamine neurotransmitters in drug addiction is one of the focuses of researchers. Elucidating the role of monoamine neurotransmitters in drug addiction will help to further understand the underlying mechanisms of drug addiction and provide a theoretical basis. This paper reviews and discusses the mechanism of action of monoamine neurotransmitters in addiction.

Mechanism of 5-Hydroxytryptamine in Drug Addiction

5-HT was first discovered in serum, also known as serotonin, and synthesized at the presynaptic terminal by tryptophan hydroxylase (TPH) using tryptophan as a precursor. In drug addiction, the effect of 5-HT is mostly achieved by regulating the DA system. The 5-HT receptor gene has polymorphisms, and most of the 14 5-HT receptors discovered are related to drug addiction, among which 5-HT1A, 5-HT1B, 5-HT2A, 5-HT3, and 5-HT4 activation can promote the release of DA, and the 5-HT2C receptor inhibits the release of DA (4, 5).

5-HT plays a critical role in opioid addiction, withdrawal symptoms, depression, and compulsive behavior. Morphine stimulates 5-HT metabolism in the nucleus accumbens (NAc) and ventral tegmental area (VTA), systemically enhances 5-HT synthesis in the brain, and increases 5-HT transport in the NAc and other brain regions (6). The transmission of 5-HT is inhibited during chronic morphine withdrawal and increasing the level of 5-HT can alleviate withdrawal symptoms, reduce the desire for morphine, reduce the concentration of 5-HT, and lead to aggravated withdrawal reactions (7, 8). 5-HT can stimulate the

release of DA: increasing the level of 5-HT in the brain can stimulate the DA system, thereby increasing the levels of DA and 5-HT transporters and increasing DA can eliminate symptoms during morphine withdrawal (9, 10). Reduced 5-HT levels lead to depression and compulsive behavior in morphine-addicted rats.

5-HT takes part in the process of amphetamine addiction. Methamphetamine can enter the nerve terminal through the 5-HT transporter, replace the 5-HT in the vesicle, thereby depleting the 5-HT in the nerve terminal (11), and at the same time, inhibit the presynaptic 5-HT reuptake transporter (serotonin transporter, SERT), reduce the reuptake of 5-HT, increase the content of 5-HT in the synapse (12), and generate CO, H2O2, and other substances, resulting in the damage of 5-HT nerve endings (13). Ecstasy (3,4-methylenedioxymethamphetamine, or MDMA) can cause synaptic 5-HT release, induce heat production and hyperactivity, deplete 5-HT, and damage nerve terminal structures (14). If MDMA was used five times within 24 hours, the concentration of 5-HT would not recover until 110 days later (15). Studies have shown that acute administration of MDMA affects the normal synthesis, operation, and metabolism of 5-HT by changing the expression of 5-HT-related genes (16).

The serotonergic system of VTA is the target of cocaine, which can block the reuptake of 5-HT and enhance the rewarding effect of cocaine (17). The 5-HT system negatively regulates the behaviors and effects of cocaine dependence. Decreasing the level of 5-HT can increase the effect of cocaine and increasing the concentration of 5-HT can weaken the effect of cocaine (18). In cocaine users, changes in 5-HT levels in the prefrontal cortex (PFC) can lead to cocaine withdrawal and craving symptoms (19). Using dopamine transporters (DAT) gene knockout mice, it was found that when the DAT function of the VTA is reduced, 5-HT plays a regulatory role, leading to cocaine-induced enhanced DA levels in NAc (17).

Mechanism of Dopamine in Drug Addiction

DA is the precursor of NE, and it is a key neurotransmitter in the hypothalamus and pituitary gland. Its increase and decrease regulate emotions, and it acts on DA D1 and D2 receptors in the brain to complete the reward effect, making people excited or depressed (20).

DA plays as the underlying contributor to the reward effect, withdrawal symptoms, drug-seeking behavior and plasticity of dopamine neurons caused by opioid addiction. Opioids can increase the release of DA in the mesolimbic DA neural pathway and can also inhibit γ-aminobutyric acid (GABA) neurons through opioid receptors, releasing GABA's effect on the ventral tegmental area. Inhibition of DA neurons in the area (VTA) increases the activity of DA neurons, resulting in a rewarding effect (21). Heroin causes DA neurons in the PFC and NAc to release DA through the unnatural reward effect, disrupting the metabolic balance of DA in the brain (22). If heroin stimulation is stopped, the amount of DA released by the nerve endings decreases, and withdrawal symptoms appear, which drives the body to look for heroin stimulation and re-establish the metabolic balance of DA (23). The drug-seeking behavior of heroin addiction is related to the regulation of DA in the ventromedial prefrontal cortex (vmPFC) (24). DA can reduce the excitability of pain excitation neurons (PEN) in morphine-addicted rats and has an inhibitory effect on PEN in the caudate nucleus (25, 26). During morphine withdrawal, the excitability of PEN increases, and the pain symptoms of morphine withdrawal become prominent (27). In morphine addiction, the plasticity of DA neurons is also altered, manifested by increased tyrosine hydroxylase (TH) activity, and these changes are associated with changes in transcription factors (28). DA levels in the VTA of rats were increased by heroin self-administration, resulting in the release of glutamate in the VTA, and the use of glutamate receptor antagonists could prevent the release of DA in relation to the concentration of glutamate (29). It was found that the DA levels in the VTA release correlate with VTA glutamate release (30).

Addiction to amphetamines such as METH leads to an increase in DA levels in the brain, resulting in reward effects, drug craving, drug-seeking behavior, behavioral sensitization, and neuronal damage (31). Amphetamines can promote the release of DA from the axon terminals of nerve cells, activate the nerve cells in the locus coeruleus (LC), striatum, hippocampus, and other brain regions, and change cognitive function, body movement, and spirit (32). As a pseudo-neurotransmitter, METH replaces endogenous DA and combines with DAT, prompting synapses to accelerate the release of DA and increase the concentration of DA in the synaptic gap, manifested as increased movement, increased alertness, and rigidity, and behaviors such as exercise, mental changes, and irritability (33). Due to the combination of METH and the monoamine transporter, the reuptake of DA is inhibited, the activity of TH is reduced, and the density of DA reuptake sites is reduced, which eventually leads to the exhaustion of DA at the ends of neurons, extreme fatigue, depression, inattention, memory loss, and other symptoms (34). The release of DA plays a role in the relapse induced by METH. The increase of DA in PFC may be one of the important reasons for mediating drug-seeking behavior and leading to relapse (35). In the late stage of withdrawal, the DA activity in the VTA region has returned to a basic level, while the striatal DA release is still at a high level, which is related to the behavioral sensitization caused by METH (36). METH causes permanent damage to DA neurons in the substantia nigra (37), and ammonia produced by METH has been proven to have long-term damage to DA neurons (38). Cannabis CB1 receptor antagonists can reduce the release of DA in the NAc caused by amphetamine, indicating that the release of DA from the NAc by amphetamine is related to the CB1 receptor of cannabis (39, 40).

Activation of the mesolimbic DA system is the neurobiological basis of cocaine addiction. Studies have shown that cocaine causes DA neurons in the VTA to release stored DA, increases the concentration of extracellular DA in DA neurons, and then leads to enhance DA release in the striatum and other nerve nuclei (41); the degree of psychomotor activation induced by cocaine is also related to the DA response (42). At the same time, cocaine blocks the re-uptake of DA by DAT (43). The mechanism is that cocaine and Na+ have the same binding site on DAT. When cocaine exists, it competes with Na+ to bind to the same site, resulting in the inability of DAT to normally combine with DA (44). DA accumulation between gaps causes the DA nerve fibers to be excited continuously, which makes the user feel pleasure (45). Acute cocaine inhibits the release of DA

from the mesolimbic system through presynaptic D2 receptors (46). Cocaine can also block DA reuptake by prolonging the transient change of DA (47). After repeated DA stimulation, the number of dendritic branches and spines of neurons increases, as does the density of synapses (48). The DA signaling pathway plays a pivotal regulatory role in cocaine-mediated neuronal dendrite remodeling, which further leads to brain addiction to cocaine. In vivo fast-scan cyclic voltammetry was used to study the changes in NAc's electrically evoked DA release caused by cocaine self-administration, and the results showed that cocaine injection could increase the electrically evoked DA release (49).

Mechanism of Norepinephrine in Drug Addiction

NE, a crucial neurotransmitter in the brain, is involved in many brain functions, including attention, arousal, learning, mood, memory, and stress response. NE plays an active role in the positive rewards of drug addiction. The acute intoxication period, long-term use, acute withdrawal after addiction, and relapse of many addictive drugs are all strongly associated with the changes in NE signals.

Mesolimbic DA neurons act as a positive reinforcement system, and LC intrinsic NE neurons act as a negative reinforcement system to participate in the opioid addiction process (50). Long-term exposure to exogenous opioids inhibits NE neurons in the LC. After stopping the administration, the activity of NE neurons in the LC increases, causing drug withdrawal symptoms (51). Meanwhile, the excitation and spontaneous discharge of NE neurons increase leading to an increased release of NE (52). Chronic morphine treatment and withdrawal cause the increase of noradrenergic neurons in the LC; the expression of NE is upregulated, the release of NE is increased, and the reuptake of NE is inhibited simultaneously (53). There is a correlation between endogenous opioid peptides and NE demonstrating as a mutual connection and a mutual restriction as well (54). It has been found that NE in the brain may be directly involved in the generation of an anxiety state after morphine withdrawal (55). NE can inhibit opioid addiction withdrawal-related pain. During opioid dependence and tolerance, the electrical activity of NE neurons in the LC is inhibited and the release of NE is reduced, so the pain symptoms of acute opioid withdrawal appear (56).

NE takes part in the process of amphetamine addiction. METH promotes the release of NE from vesicles to the interstitium, and inhibitors of NET inhibit the transport of NE, increasing the concentration of extracellular NE in the striatum and hippocampus (57, 58). Studies have shown that there is a dose-related relationship between the intake of amphetamines and the release of NE by the human body, indicating that the main function of amphetamines may be to stimulate the release of NE by the human body. In the impulsive behavior induced by amphetamine, increasing the level of endogenous NE can reduce impulsive behavior but has no effect on decision-making behavior (59, 60).

Cocaine is a NE reuptake inhibitor, which inhibits the reuptake of NE and enhances the rewarding effect (61). Cocaine acts on the NET via modulating the acute release of NE, and preventing the NET from transporting presynaptically released NE back to the presynaptic nerve terminal (62). Cocaine inhibits the activity of NE monoamine oxidase and prevents the decomposition of NE (63). NE acts as a signal substance in the striatum and amygdala, leading to the anxiety-induced behavior of cocaine (64). The good side is that cocaine drug-seeking cravings can be blocked by NE reuptake inhibitors (65).

Conclusion

The monoamine neurotransmitters 5-HT, DA, and NE play a substantial role in the reward effect of drug addiction, withdrawal symptoms, drug craving, anxiety, depression, and compulsive behavior. The mechanism of drug dependency is intricate. The release and corresponding effects of monoamine neurotransmitters are different for various addictive drugs, different stages of addiction, and different brain regions. There are few studies on the release of monoamine neurotransmitters in different stages of drug addiction, and the role of monoamine neurotransmitters released by different addictive drugs in the corresponding drug addiction needs further study. Using optogenetics, it was found that the activation of dopaminergic neurons is conducive to the development of positive reinforcement in the process of seeking reward effects (66), and meanwhile, it was found that the neuron signals of the dorsal raphe nucleus achieve reward effects through 5-HT (67). Using new technologies and methods to study monoamine neurotransmitters and gain an in-depth understanding of the role of monoamine neurotransmitters in drug addiction will not only help to further understand the mechanism of drug addiction but also provide a basis for the development of therapeutic strategies.■

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