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Advances in the Study of Neural Mechanisms Associated with Exercise to Ameliorate Nicotine Addiction

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Abstract

Objective: The objective is to elucidate the effectiveness of exercise as smoking cessation aid by sorting out the neurotransmitter basis of nicotine addiction and combining it with the neurotransmitter modulation effect of exercise, and finally to organize and analyze the mechanisms related to exercise to ameliorate nicotine addiction. **Methods:** We searched the Web of Science and PubMed databases for keywords, including "nicotine addiction", "exercise", "sports", "physical activity", "smoking cessation" and "tobacco withdrawal", and compiled and analyzed the relevant literature to explain the neurobiological mechanisms of nicotine addiction and the effects of exercise on ameliorating nicotine addiction and related mechanisms. **Results:** 1) long-term nicotine intake, on the one hand, binds to acetylcholine receptors to produce rewarding effects, and on the other hand, causes rewarding effects by regulating the release of various neurotransmitters and signaling, making smokers feel pleasure and experiencing withdrawal symptoms after stopping smoking; 2) exercise can effectively ameliorate nicotine addiction; 3) exercise reduces the desire to smoke by activating the reward system to cause the body to release dopamine, partially replacing the rewarding effects and reducing withdrawal symptoms. **Conclusion:** Exercise is effective in ameliorating nicotine addiction through the modulation of neurotransmitters and improves the health status of people who quit smoking. Therefore, physical activity and physical exercise during smoking cessation are recommended to reduce nicotine withdrawal symptoms and smoking cravings.

Keywords

Nicotine Addiction, Reward Effect, Smoking Cessation, Acetylcholine,

Midbrain Limbic Dopamine, Withdrawal Response, Exercise

1. Introduction

Smoking is a major public health problem that causes diseases and deaths worldwide, and the act of smoking not only harms active smokers, but also exposes passive smokers to equally serious health risks, and is an independent risk factor for diseases such as lung cancer, chronic bronchitis, and emphysema (Vannimenus et al., 2018). The smoke particles in cigarettes are the main harmful substances that spread from the lungs to the bloodstream and then to all organs of the body, and 70 of these chemicals are known as carcinogens (Warner & Schroeder, 2017). In addition, smoking is a major cause of cancer, cardiovascular disease, diabetes, and many other diseases, and quitting can reduce the risk of these major chronic diseases and increase life expectancy (Hu et al., 2018). Nicotine is the main active ingredient of tobacco, and nicotine addiction refers to the phenomenon that smokers develop progressive physical and mental dependence during long-term smoking. Long-term intake of nicotine alters and disrupts the brain's ability to process information, and produces tolerance, dependence, and obvious withdrawal symptoms, such as depression, restlessness, lack of concentration, and increased feelings of stress (Sharp & Chen, 2019).

However, for long-term smokers, the sudden cessation of smoking tends to produce withdrawal symptoms, and the reward dysregulation and nicotine attention bias are usually associated with nicotine addiction, resulting in frequent relapse after quitting, so most people who try to quit end up failing (Livingstone-Banks et al., 2019). Smoking is by nature highly recurrent addictive behavior, and nicotine dependence is the primary cause of addiction. Nicotine builds and maintains tobacco addiction through a complex effect on the brain's neurochemical reactions, and tobacco control through external measures does not get to the root of the problem (Benowitz, 2010). Currently, the commonly used methods for quitting smoking are mainly based on pharmacotherapy and nicotine replacement therapy, but they have certain side effects and recurrence. Exercise can reduce nicotine dependence while improving the health status of people who quit smoking, effectively reducing smokers' craving for cigarettes and withdrawal symptoms, and increasing the success rate of quitting smoking, so it is considered an important non-pharmaceutical therapy (Brynildsen et al., 2018; Zhou & Zhou, 2018; Ussher et al., 2019). This study illustrates the effectiveness of exercise as the aid to smoking cessation by sorting out the neural mechanisms associated with nicotine addiction, combining the effects of exercise on the regulation of neurotransmitters, and organizing and analyzing the mechanisms associated with exercise to ameliorate nicotine addiction.

2. Mechanism of Nicotine Addiction

There are many nerve cells in the human brain that have evolved to form a loop

area responsible for feeling arousal, learning to remember and actively repeating behaviors to obtain pleasure, called the "reward system", and activating and reinforcing behaviors are the two main functions of the reward system (Hu, 2016). The effects of addictive substances on the body are mainly characterized by higher reward effects than common substances, the potential to induce new brain pathways (characterized by symptoms such as unpleasant withdrawal reactions), and the ability to induce adaptive changes in the nervous system at the tissue, cellular, molecular and genomic structural levels, mainly in the form of decreased dopamine receptor activity in the reward system (de Baat et al., 2020). The dopamine D2 receptor activity is reduced in the bilateral striatal regions of the brain in patients with tobacco addiction, and their addictive behavior may be a compensatory and compulsive phenomenon of the body to maintain the balance of dopamine (DA) receptors in the body (Fehr et al., 2008). The neuroplasticity changes caused by addictive substances mainly occur in brain areas involved in learning and memory, such as the Ventral Tegmental Area (VTA), Nucleus Accumben (NAc), and Prefrontal Cortex (PFC), etc. Most addictive substances can increase the synaptic density of VTA and NAc, but the plasticity changes caused by different addictive substances and the regulatory mechanisms vary (Niehaus et al., 2009).

2.1. Nicotine Binds to Acetylcholine Receptors to Produce a Rewarding Effect

The most closely associated with nicotine dependence is the midbrain limbic dopamine reward system, consisting mainly of the ventral tegmental area, the nucleus ambiguous, the prefrontal cortex, and the amygdala, which, in addition to being involved in motor regulation, are also closely associated with drug dependence and mental activity (Feng, 2015). Acetylcholine (ACh) is a member of the superfamily of ligand-gated ion channels that are widely distributed throughout the nervous system and systemic tissues (Jia et al., 2013; Papke 2014). The nicotine-binding acetylcholine receptors in the CNS are known as nicotinic acetylcholine receptors (nAChRs), and they are the major subtype of ACh receptors. The nAChRs play an important role in neuromuscular transmission and signaling in the central and peripheral nervous system by binding to the endogenous neurotransmitter acetylcholine or exogenous ligands such as nicotine (Albuquerque et al., 2009). Nicotine, the main component of tobacco, promotes the release of acetylcholine by stimulating nAChRs located in the brain. Prolonged nicotine intake may lead to compensatory adaptation of its receptor function (e.g., receptor desensitization), which alters the cellular signaling cascade responses involved in learning, resulting in impaired cognitive performance, nicotine dependence, and smoking cravings in smokers. Nicotine ingested with tobacco can enter the brain through the Blood-Brain Barrier (BBB) and act on the widely distributed nAChRs in the brain, stimulating neurons in the ventral tegmental area of the midbrain. When nerve impulses are transmitted to nerve endings, acetylcholine in synaptic vesicles is released into the synaptic gap and binds to nAChRs on the postsynaptic membrane, causing a potential change in postsy-

naptic neurons, opening ion channels, stimulating the release of dopamine, producing a sense of pleasure, and ultimately reinforcing smoking behavior (Albuquerque et al., 2009; Gozen et al., 2016; Wang et al., 2017; Lei et al., 2019). In addition, nicotine stimulates the midbrain limbic and midbrain frontal DA systems, resulting in enhanced DA release in this region, neural pulse firing, and increased neuronal excitability (Bono et al., 2019).

In addition, nicotine in the body can cause rewarding effects by modulating the release and signaling of a variety of central neurotransmitters, including norepinephrine (NE), 5hydroxytryptamine (5-HT), glutamate (Glu), and gamma-aminobutyric acid (GABA) (Tiwari et al., 2020).

2.2. Nicotine Desensitizes Acetylcholine Receptors to Produce Withdrawal Symptoms

During continuous smoking in smokers, nicotine binds rapidly to acetylcholine receptors. Because the half-life of nicotine in the body (the time it takes for the body to metabolize half the dose) is as long as 2 hours, leaving nAChRs exposed to nicotine for long periods, acetylcholine is unable to react with sufficient numbers of receptors, resulting in the inactivation of most nAChRs and desensitization (Hopkins et al., 2012). To ensure the normal transmission of nerve signals, the body produces more nAChRs to bind to acetylcholine, resulting in a continuous upregulation of the number of nAChRs (Hopkins et al., 2012). In addition, chronic nicotine exposure leads to many neurological adaptations, such as the upregulation of nAChR subunits, and withdrawal syndrome occurs when nicotine is no longer present, for example, during attempts to quit smoking (Wittenberg et al., 2020). Therefore, if a smoker is in a state of withdrawal, or has not smoked for a long time (for example, during exercise or sleep), the nicotine in the body will be gradually consumed, when the original nAChRs combined with nicotine and acetylcholine combined, the number of nAChRs in the body is much larger than the number of acetylcholine, so that the nerve signaling disorder, the body appears a variety of discomfort, such as insomnia, anxiety, increased appetite, weight gain, spitting gray-black spit, arrhythmia, increased blood pressure and other phenomena, these symptoms are what we often call "withdrawal reaction" (Wittenberg et al., 2020; Masiero et al., 2020: p. 8).

From the above, it is clear that for long-term smokers, on the one hand, ingested nicotine binds to nAChRs *in vivo*, upregulating their number and desensitizing them, leading to withdrawal reactions and smoking cravings after quitting, while nicotine exposure causes Ach discharge and stimulates dopamine release; on the other hand, nicotine directly stimulates the ventral tegmental area of the midbrain causing increased dopamine release and producing a rewarding effect.

3. Exercise Improves Nicotine Addiction

Exercise is an easily accessible, low-cost treatment that can alleviate nicotine with-

drawal symptoms and cravings, and is an adjunct to smoking cessation while promoting physical and mental health and improving the quality of life of smokers (Liu et al., 2019a). Loprinzi et al. found that maintaining regular physical activity among long-term smokers may help in quitting smoking through follow-up observations (Loprinzi & Walker, 2016). In addition, Purani et al. tested and analyzed the sleep of 32 subjects and found that an increase in exercise during the same period improved sleep quality, and that better sleep quality was associated with withdrawal symptoms and reduced desire to smoke (Purani et al., 2019).

Researchers exploring the effectiveness of different exercise modalities for smoking cessation found that aerobic exercise is one of the exercise modalities that are effective in improving nicotine addiction. Masiero et al. found that brief periods of moderate-intensity exercise rapidly reduced withdrawal discomfort and the desire to smoke (Masiero et al., 2020: p. 8). Abrantes et al. found that daily smokers experienced reduced anxiety and decreased nicotine cravings after 12 weeks of an exercise intervention of increasing intensity (Abrantes et al., 2018). In addition, physical activity can help enhance the emotional experience and improve the likelihood of quitting, especially for smokers suffering from depression (Abrantes et al., 2017). Several studies have shown that yoga also has a positive impact on quitting smoking. Rosen et al. found that subjects felt less stress, better breathing, and an increased sense of well-being after an 8-week yoga intervention, suggesting that yoga could be an adjunctive treatment for nicotine addiction, especially for light smokers (Rosen et al., 2016; Bock et al., 2019). Researchers have explored the effectiveness of anaerobic-fed exercise for smoking cessation and found that anaerobic exercise improves the efficiency of smoking cessation. Cheung et al. found that simple grip strength exercises, isometric exercises were effective in quitting smoking and ensured better compliance without providing incentives or coercive measures; and when exercise compliance was higher, the success rate of quitting smoking was higher (Cheung et al., 2020). In addition, Zvolensky et al. showed that high-intensity exercise (77% - 85% VO_{2max}, 25 min/time, 3 times/week for 15 weeks) can help quitters reduce anxiety and negative emotions while quitting smoking, which can help increase the success rate of quitting smoking (Zvolensky et al., 2018). In addition, High-Intensity Interval Training (HIIT) is a mix of high-intensity exercise and low-intensity intervals that can improve smoking cessation symptoms and other chronic diseases caused by smoking. Researchers have also explored and analyzed the effects of HIIT on smoking cessation. A study by Pavey et al. found that the HIIT group (treadmill running, 4 minutes of high intensity at 85% - 95% of maximum heart rate with 3-minute recovery intervals for 4 sets totaling 35 minutes each, 3 times/week for 26 weeks) was better at achieving the smoking cessation intervention compared to the control group (10,000 steps per day) (Pavey et al., 2015). After a 12-week follow-up survey of subjects who used HIIT as a smoking cessation method, we found that HIIT was effective and that quitters were sa-

tisfied, suggesting that HIIT was generally accepted by quitters to some extent (Allen et al., 2018).

In conclusion, aerobic exercise has a good effect on smoking cessation and is a low-threshold form of exercise that can be widely applied to the smoking cessation population, but has certain venue requirements and needs to be performed over a long time. High-intensity anaerobic exercise can improve the efficiency of exercise interventions for smoking cessation, but its long-term effects need to be further explored. High-intensity interval training, because of its mixed energy supply, can achieve the goal of effective smoking cessation while improving cardiorespiratory function and health.

4. Mechanisms of Exercise to Quit Smoking

4.1. Exercise Reduces the Desire to Smoke by Activating the Limbic Reward System in the Midbrain

The dopamine that constitutes the limbic reward system in the midbrain is mainly derived from dopamine neurons in the ventral tegmental area of the brain, and its quantitative changes underlie the formation and consolidation of addictive behaviors (Correa et al., 2020). Increased dopamine release in the nucleus ambiguous is a key mechanism for initiating and maintaining nicotine addiction, and increased dopamine in the prefrontal cortex is thought to be critical for modulating the cognitive-enhancing effects of nicotine (Herman et al., 2014). Nicotine increases smokers' pleasure, which leads to addictive behavior (Bono et al., 2019). Exercise can produce the same pleasurable feelings in smokers and can therefore help them quit. Studies have shown that exercise training increases mRNA levels of Tyrosine Hydroxylase (TH) in the ventral tegmental area and increases mRNA expression of Delta-Opioid Receptors (DOR) in the nucleus, thereby promoting DA release and increasing DA synthesis, enhancing DA neurotransmission, partially replacing nicotine-induced reward effects, and modulating reward circuits to counteract addictive behaviors (Greenwood et al., 2011; Flack et al., 2019). In addition, exercise activates vagal sensing of dopamine, increases serum dopamine levels, and reduces systemic inflammation, resulting in unique adaptations of dopamine circuits in the limbic and substantia nigra striata of the midbrain involved in motor behavior and the occurrence of rewarding effects, thus ameliorating mechanisms of nicotine addiction associated with enhanced cortical plasticity and dopamine release (Greenwood, 2019; Shimojo et al., 2019). Exercise stimulates the production of dopamine in the midbrain limb, which results in a significant reduction in the desire to smoke after exercise (Van Rensburg et al., 2012). Thus, exercise can help quitters improve nicotine addiction by activating the brain's reward system to reduce the desire to smoke.

4.1.1. Exercise to Activate the Reward System by Adding BDNF

Brain-Derived Neurotrophic Factor (BDNF) is a small-molecule dimeric protein that belongs to the family of neurotrophic growth factors (Leibrock et al., 1989).

As the most abundant neurotrophic factor in the brain, BDNF is densely expressed in the central and peripheral nervous system, with higher concentrations in the hippocampus and cerebral cortex (Conner et al., 1997). It has been shown that the concentration of BDNF in the CNS is closely related to the concentration of BDNF in the serum, and changes in serum BDNF concentration levels indirectly reflect changes in BDNF in the CNS (Klein et al., 2011). Since it is difficult to directly measure brain BDNF levels in population experiments, serum BDNF is often used as a proxy for brain BDNF (Huang et al., 2020). BDNF plays a potential role in nicotine addiction, and nicotine intake can increase serum BDNF levels (Hyman et al., 1991; Mössner et al., 2000; Carvalho et al., 2008). Nicotine exposure (DE) impairs hydrolysis of proBDNF protein in serum and leads to a proBDNF-BDNF imbalance in the central nervous system (Buck et al., 2019). After repeated exposure to nicotine, dopaminergic neurons increase DA release via nAChR, and DA binding to its receptor DR activates phosphorylation of CREB, which further upregulates mRNA expression of BDNF, thereby increasing BDNF expression. Increased BDNF activates TrkB, and enhanced phosphorylation of TrkB further activates downstream protein kinase signaling pathways such as Ras/MEK, PI3K/Akt and PLCγ/CaMKII signaling pathways. These protein kinases exert positive feedback, translocate to the nucleus and reactivate CREB phosphorylation, increasing transcription of BDNF genes (Huang et al., 2020). Studies have shown that exercise can activate the BDNF signaling pathway by altering the mBDNF/proBDNF ratio in serum, increasing BDNF levels, which in turn replaces the rewarding effects of nicotine and ultimately reduces the desire to smoke (Zoladz & Pilc, 2010; Luo et al., 2019).

4.1.2. Exercise Activates the Reward System by Increasing Endorphins

Endogenous Opioid-Like Substances (OLS) are naturally occurring opioid-like active substances in mammals, including opioid peptides and non-peptide morphine-like substances. Endorphins (EP) are endogenous morphine-like peptide hormones containing alpha, beta, and gamma isoforms that are involved in the production of rewarding pleasure and emotion regulation in the addiction circuit, producing a drug-like euphoria (Trigo et al., 2010; Bodnar, 2021). EP is the main regulator of the rewarding effect of the organism, and β-EP has a mutually reinforcing effect with the limbic dopamine system of the midbrain, the center of the rewarding system of the organism. Endorphins activate CB1 and/or CB2 receptors to regulate various physiological functions, and the distribution of these receptors in the CNS and periphery correlates with their role in the control of motor function, stress response, analgesia, and rewarding effects (Vlachou & Panagis, 2014; Ligresti et al., 2016; Spanagel, 2020). Exercise stress can cause a sustained response to EP in several sites, including the basal hypothalamus and solitary nucleus of the medulla oblongata, by increasing body temperature, enhancing energy metabolism, activating the Hypothalamic-Pituitary-Adrenal (HPA) axis, and altering plasma ion concentrations (Spanagel, 2020). Exercise leads to a significant increase in the concentration of endogenous opioid peptides, especially beta-endorphin and be-

ta-lipoprotein, causing euphoria and reducing tension and anxiety (Bodnar, 2021). It has been shown that table running exercise can cause an increase in β-EP in the gray matter of the hypothalamus of rats, as well as a significant increase in β-endorphin-positive products in the hippocampus; in addition, β-endorphin is released from immune cells containing β-endorphin in the plasma during exercise, increasing serum levels of β-endorphin (Persson et al., 2004; Wu & Liu, 2004). β-EP inhibits GABAergic neurons by binding to mu-opioid receptors, thereby de-inhibiting DAergic neurons and promoting the release of DA from brain regions such as the nucleus accumbens (the main brain region of the reward circuit), activating the reward effect and triggering euphoria (Fichna et al., 2007).

4.2. Exercise Reduces Nicotine Withdrawal Symptoms by Modulating Central Neurotransmitters

As mentioned earlier, once nicotine addiction has set in, the act of smoking is not just about getting pleasure, but more about avoiding discomfort in the organism; therefore, alleviating withdrawal symptoms and adverse reactions is the key to successful smoking cessation. Several studies have demonstrated that exercise can increase the success of quitting by reducing withdrawal symptoms by increasing positive mood, controlling weight, and improving sleep quality, as well as reducing anxiety, depression, and memory loss in smokers. Exercise can reduce nicotine withdrawal symptoms by modulating the release and signaling of multiple central neurotransmitters. In a study in a mouse model, Keyworth et al. found that the severity of withdrawal symptoms was significantly reduced in nicotine-treated mice after rotarod exercise and that α7 nAChR binding to acetylcholine was significantly upregulated in the hippocampal CA2/3 region, a finding that explains the modulatory effect of exercise on nicotine withdrawal symptoms and the mechanism of amelioration (Keyworth et al., 2018).

4.2.1. Exercise Reduces Withdrawal Symptoms by Regulating 5-Hydroxytryptamine

5-Hydroxytryptamine (5-HT) is a mood-altering neurotransmitter, often referred to as "serotonin", which can affect a person's appetite, internal drive (appetite, sleep, sex), and mood. Nicotine in cigarettes can keep 5-HT at high levels in the body, and 5-HT can activate the limbic dopamine system in the midbrain after acting on its receptors, producing a rewarding effect and keeping people happy (Bo, 2013; Murphy et al., 2020; Jiao et al., 2021). Nicotine increases 5-HT release from rat striatal synapses and its transmission positively regulates reward processes in the brain but does not increase release from cortical or hippocampal synaptosomes (Hou et al., 2014). It has been shown that smoking a cigarette or chewing nicotine gum can cause a transient increase in 5-HT levels in platelets compared to non-smokers (Lowery et al., 2017). This suggests that nicotine intake increases the release of 5-HT in nonsmokers, which in turn modulates the rewarding process in the brain. Park et al. showed that treadmill exercise increased 5-HT expression in nicotine withdrawal rats, thereby reducing anxiety, depression,

and memory loss induced by nicotine withdrawal (Park et al., 2019). 5-HT receptors are essential for exercise-induced hippocampal neurogenesis, and exercise can promote cell proliferation by activating 5-HT receptors and can increase BDNF levels in hippocampal tissue and improve anxiety, thereby reducing the stage symptoms that arise after long-term smokers stop smoking and reducing the desire to smoke (Lee et al., 2016).

4.2.2. Exercise Reduces Withdrawal Symptoms by Regulating Gamma-Aminobutyric Acid

Gamma-Aminobutyric Acid (GABA) is the main inhibitory neurotransmitter in the brain, and its main role is to regulate the excitability of neurons and the secretion of other neurotransmitters through GABA receptors, which helps reduce stress and eliminate anxiety (Luo & Liang, 2008; Thomas et al., 2018; Liu et al., 2019b). Studies have shown that chronic administration of nicotine can significantly reduce the levels of G proteins coupled to GABA receptors without altering the density and affinity of GABA receptors, which may attenuate the degree of inhibition of limbic dopamine neurons in the midbrain cortex, leading to a highly sensitive reward effect in the body during prolonged exposure to nicotine (Varani et al., 2018). Exercise can regulate the balance between EPSPs and IPSPs in the motor cortex by inhibiting GABA receptors and upregulating the expression of BDNF proteins in the motor cortex, which ultimately promotes neuroplasticity and reduces withdrawal symptoms after smoking cessation (Takahashi et al., 2017). Aerobic exercise enhanced inhibitory synaptic transmission efficacy and ameliorated nicotine addiction-induced DA neuronal hyperactivation by increasing presynaptic GABA release from VTA dopamine neurons in nicotine-addicted mice, which may be one of the central mechanisms to ameliorate nicotine addiction through exercise (Thomas et al., 2018).

4.2.3. Exercise Reduces Withdrawal Symptoms by Regulating Glutamate

Nicotine acts on glutamatergic efferent nerve fibers emanating from the prefrontal cortex, promoting the release of glutamate (Glu) from the ventral tegmental area, which in turn acts on N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors in DAergic neurons (on the postsynaptic membrane), increasing their firing frequency and producing a rewarding effect (Delibas et al., 2005; Deehan et al., 2015). In addition, nicotine can cause long-duration excitation of glutamatergic neurons while inhibiting GABA neural signaling, thus indirectly stimulating DA neurons in the ventral tegmental area, resulting in increased DA release in the nucleus accumbens and prefrontal cortex, producing a rewarding effect and ultimately leading to the formation of tobacco addiction (Gao et al., 2010). Exercise prevents overstimulation of glutamate receptors due to chronic nicotine intake, increases glutamate receptor activity, and reduces glutamate concentration in the striatum by modulating RGS4 and CB1 expression in the striatum, with different effects of exercise on glutamate receptor activity and plasticity for different cycles of intervention (Fischer-Smith et al., 2012; Lin et al., 2017).

In summary, exercise activates vagal sensing of the dopamine system, reduces systemic inflammation, increases serum dopamine levels, partially replaces the rewarding effect, and reduces the desire to smoke in smokers. In addition, by promoting the binding of acetylcholine to its receptors in the body and regulating the expression of Glu, GABA, and 5-HT in the body, exercise increases the positive mood of quitters, reduces their withdrawal symptoms such as anxiety, depression, and memory loss, and controls weight gain and improves sleep quality, which ultimately leads to a reduced desire to smoke and improved nicotine addiction.

5. Problems and Shortcomings of the Current Study

Nicotine addiction is a major public health problem in the world today, and exercise interventions can compensate for the shortcomings of other smoking cessation methods (such as the side effects of smoking cessation medications) while achieving good cessation results. Neurotransmitters may be important targets for exercise to improve nicotine addiction, and exercise may improve nicotine addiction by modulating the expression of various neurotransmitters. However, there are certain shortcomings in the research on exercise interventions for nicotine addiction that hinder the large-scale use of exercise training for tobacco addicts.

1) It is not clear the effect of exercise intensity and duration in suppressing nicotine addictive behavior.

2) Valid and objective biomarkers of improvement in nicotine addiction have not been identified, so quantitative analysis of improving outcomes is not possible.

3) The mechanisms of nicotine addiction are complex and attention should be paid to other neural tissues in addition to the ventral tegmental area of the midbrain and the prefrontal cortex to gain a more comprehensive understanding of the ameliorative effects of exercise on nicotine addiction.

4) The dopamine reward effect induced by neurotransmitter changes is closely related to nicotine addiction, but other pathways may also be involved in the nicotine addiction process, but there are few relevant studies, which can be explored in-depth in future studies.

6. Summary

In summary, nicotine produces pleasure primarily through activation of the reward system and causes nicotine dependence and smoking cravings in smokers by modulating the release and signaling of multiple neurotransmitters. As the research on the integration of physical medicine continues to improve, and the related tools become mature, exercise intervention is becoming a practical feasible, safe and effective way to quit smoking. Exercise can be effective in ameliorating nicotine addiction by modulating neurotransmitters that activate the reward system to release dopamine, giving quitters a sense of pleasure which is similar to

smoking, partially replacing the reward effect. In addition, different exercise modalities can all reduce the desire to smoke and negative emotions of nicotine addicts to some extent and improve their physical and mental health. Therefore, exercise can be an effective intervention for smoking cessation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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